

Supporting Information

Antibacterial Activity of Metergoline Analogues: Revisiting the Ergot Alkaloid Scaffold for Antibiotic Discovery

Jarrold W. Johnson,[†] Michael J. Ellis,[†] Zoë A. Piquette,[†] Craig MacNair, Lindsey Carfrae, Timsy Bhando, Nikki E. Ritchie, Paul Saliba, Eric D. Brown,* and Jakob Magolan*

Department of Biochemistry and Biomedical Sciences and the Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario L8S 3Z5, Canada

[†] These authors contributed equally.

* e-mail: magolanj@mcmaster.ca; ebrown@mcmaster.ca

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Supplementary Figures and Tables

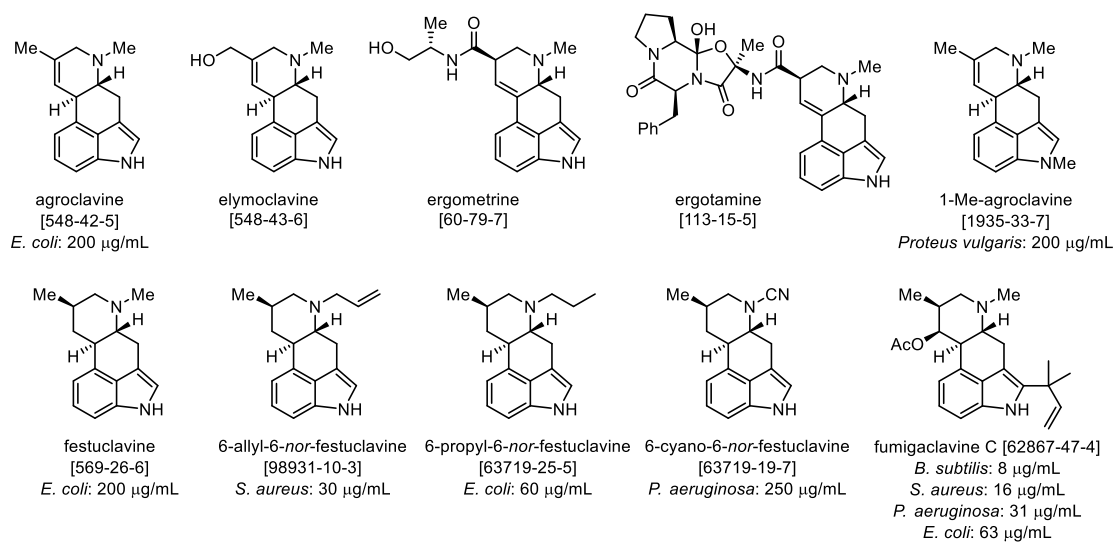


Figure S1. Antibacterial activities of natural and semisynthetic ergot alkaloids.^{1,2} Eich and Pertz also report that agroclavine showed “pronounced inhibition” of *Streptomyces purpurascens* growth, but elymoclavine was less active and the lysergic acid amides ergometrine and ergotamine were inactive.¹

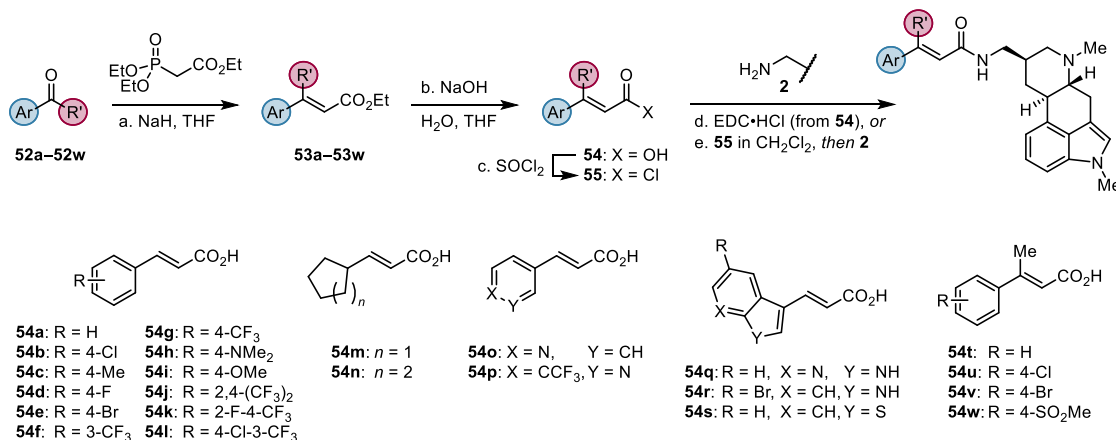


Figure S2. Synthesis of cinnamide- and β-substituted acrylamide analogues of metergoline. Many of the amide analogues were prepared by coupling commercial cinnamic acids **54** to amine **2** using EDC·HCl (General Procedure A). In some cases, carboxylic acids **54** were converted to their corresponding acid chlorides **55** and reacted with amine **2** (General Procedure B). Many of the acrylic acids not commercially available were prepared via Horner–Wadsworth–Emmons (HWE) olefinations, followed by alkaline hydrolysis (General Procedure C). Acids **54q–54s** were prepared from aldehydes **52q–52s** using malonic acid with pyridine and piperidine (General Procedure D).

1. Eich, E.; Pertz, H. Antimicrobial and antitumor effects of ergot alkaloids and their derivatives. In *Ergot: The Genus Claviceps*, Kren, V.; Cvak, L., Eds. 1999, pp. 441–449. Harwood Academic Publishers, Amsterdam, The Netherlands (doi:10.1201/9780203304198).
2. Pinheiro, E. A. A.; Carvalho, J. M.; dos Santos, D. C. P.; Feitosa, A.; Mirinho, P. S. B.; Guilhon, G. M. S.; de Souza, A. D. L.; da Silva, F. M. A.; Marinho, A. M. Antibacterial activity of alkaloids produced by endophytic fungus *Aspergillus* sp. EJC08 isolated from medical plant *Bauhinia guianensis*. *Nat. Prod. Res.* **2013**, 27, 1633–1638 (doi:10.1080/14786419.2012.750316).

Table S1. Bacterial Strains Used in This Study.

Strain		Description	Reference or Source
<i>Salmonella enterica</i> ser. Typhimurium (S. Tm)	WT	SL1344, Str ^R	Lab stock
	$\Delta tolC$	SL1344 $\Delta tolC::cm$, Str ^R	Ellis et al. ³
<i>Escherichia coli</i> K-12	WT	MG1655	Lab stock
	λpir	Host strain for plasmids with R6K γ origin	Kvitko et al. ⁴
	GKCW102	BW25113 <i>attTn7::mini-Tn7T (kan araC P_{araBAD}-fhuAC/4L)</i>	Helen Zgurskaya (U. Oklahoma). ⁵
	$\Delta tolC$ pore	MG1655 $\Delta tolC::FRT attTn7::mini-Tn7T$ (<i>gent P_{BBa_J23104}-fhuAC/4L</i>)	This study
<i>Escherichia coli</i>	EHEC	<i>E. coli</i> O157:H7 EDL933W $\Delta stx2A::kan$, Str ^R	Karen Maxwell (U. Toronto)
<i>Acinetobacter baumannii</i>	C0015	Clinical isolate. Resistant to: ^a ampicillin, amoxicillin clavulanic acid, cefazolin, cephalothin, cefixime, nitrofurantoin, cefoxitin	Gerry Wright (McMaster U.)
<i>Burkholderia cenocepacia</i>			Lab stock
<i>Klebsiella pneumoniae</i>	ATCC43816		Lab Stock
<i>Pseudomonas aeruginosa</i>	PAO1		Lab Stock
<i>Staphylococcus aureus</i>	MRSA	Canadian isolate of USA300 (CMRSA10)	Lab Stock, Christianson et al. ⁶
	MSSA	Newman	Lab Stock
	C0621	Clinical isolate. Resistant to: ^a ciprofloxacin, cefotaxime, erythromycin, levofloxacin, imipenem, oxacillin, benzylpenicillin, moxifloxacin, clarithromycin, cefaclor, azithromycin, ceftriaxone, cefuroxime	Gerry Wright (McMaster U.)
<i>Bacillus subtilis</i>	168		Lab Stock
<i>Mycobacterium smegmatis</i>	ATCC607		Lab Stock

^a Antibiotic resistance determined by CLSI guidelines in a clinical microbiology lab.

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Table S2. Plasmids and Primers Used in This Study.

Plasmid	Description	Reference or Source
pUC18R6K-mini-Tn7T-Gm	Suicide delivery vector Gm ^R Amp ^R	Choi et al. ⁷
pUC18-R6k-mini-Tn7T-Gm- <i>fhuAC/4L</i>	pUC18 mini-Tn7T vector containing the constitutive <i>fhuAC/4L</i> gene; Gm ^R Amp ^R	This study
pTNS2	Helper plasmid for Tn7 transposase expression	Choi et al. ⁷
Primer	Sequence	
FP FhuA const BamHI	5'-ATAGGATCCTTGACAGCTAGCTCAGTCCTAGGTATTGTGCTAGCACCCGTT TTTTTGGGCTAGAAATAATTTGTTTAACTTTAA-3'	
RP FhuA const KpnI	5'-TATGGTACCTTAGAAACGGAAGGTTGCGGT-3'	

Experimental Procedures

Bacterial Strains and Culture Conditions

Strains, plasmids, and primers used in this study are listed in Table S1 and Table S2. Bacteria were routinely propagated in LB media (10 g/L NaCl, 10 g/L tryptone, 5 g/L yeast extract). For MIC and checkerboard experiments, overnight cultures were inoculated with a single colony in cation-adjusted MHB (BBL Mueller–Hinton Broth, cation-adjusted) and subcultured 1:100 into MHB or the indicated assay media: LPM (5 mM KCl, 7.5 mM (NH₄)₂SO₄, 0.5 mM K₂SO₄, 0.2% [w/v] glucose, 49 μM MgCl₂, 337 μM PO₄³⁻, 4 μg/mL histidine, 80 mM MES, pH 5.8), MOPS glucose minimal media (Teknova), cation-adjusted MHB with 10 mM EDTA, cation-adjusted MHB with 10 μg/mL SPR741 (a gift from SPERO Therapeutics).

The hyperpermeable strain, *E. coli* Δ *tolC* pore, was constructed as described below. The Δ *tolC::kan* allele from the corresponding Keio collection strain⁸ was moved into *E. coli* MG1655 with P1 transduction. The kanamycin resistance cassette was eliminated by transforming the transduced strain with pCP20,⁹ followed by curing the plasmid by growing clones at 42 °C in the absence of antibiotic selection. Clones were verified by colony PCR and antibiotic susceptibility testing for common TolC efflux substrate. The *fhuAC/4L* gene was amplified from *E. coli* GKCW102 (a gift from Helen Zgurskaya, U. Oklahoma).⁵ FhuAC/4L in this strain is expressed under the control of arabinose-inducible promoter. In order to have the constitutive expression of FhuAC/4L, we used the synthetic promoter BBa_J23104 (iGem Registry).¹⁰ *fhuAC/4L* was amplified from *E. coli* GKCW102 using sequence-specific primers (Table S2) such that the forward primer contained the BBa_J23104 promoter sequence. The PCR product was cloned into the suicide vector pUC18-R6K-mini-Tn7T-Gm (Addgene) and transformed into *E. coli* λ *pir*.⁴ The constitutive *fhuAC/4L* gene was then inserted into the *E. coli* MG1655 Δ *tolC* strain using a

7. Choi, K. H.; Schweizer, H.P. mini-Tn7 insertion in bacteria with single *attTn7* sites: Example *Pseudomonas aeruginosa*. *Nat. Protoc.* **2006**, *1*, 153–161 (doi:10.1038/nprot.2006.24).
8. Baba, T.; Ara, T.; Hasegawa, M.; Takai, Y.; Okumura, Y.; Baba, M.; Datsenko, K. A.; Tomita, M.; Wanner, B. L.; Mori, H. Construction of *Escherichia coli* K-12 in-frame, single-gene knockout mutants: the Keio collection. *Mol. Syst. Biol.* **2006**, *2*, 2006.0008 (doi:10.1038/msb4100050).
9. Datsenko, K. A.; Wanner, B. L. One-step inactivation of chromosomal genes in *Escherichia coli* K-12 using PCR products. *Proc. Natl. Acad. Sci., U.S.A.* **2000**, *97*, 6640–6645 (doi:10.1073/pnas.120163297).
10. MIT: Registry of Standard Biological Parts: <http://parts.igem.org/Promoters/Catalog/Anderson>.

mini-Tn7T-based protocol.⁷ The pUC18-R6K-Tn7T-Gm-FhuA construct was electroporated into *E. coli* MG1655 $\Delta tolC$ strain along with the pTNS2 helper plasmid, outgrown for 1 h at 37 °C in SOC media, and then plated on LB containing gentamicin. Insertions were confirmed with PCR and antibiotic susceptibility testing with vancomycin and azithromycin.⁵

Minimum Inhibitory Concentration (MIC) and Checkerboard Broth Microdilution Assays

Bacterial overnight cultures were inoculated from a single colony into MHB, and subcultured 1:100 into the indicated assay media and grown to mid-log phase (OD_{600} 0.3–0.5). Cultures were diluted 1000-fold into the indicated assay media for a starting inoculum of $\sim 1 \times 10^5$ cfu/mL and either 150 μ L (96-well plate) or 50 μ L (384-well plate) of this dilution was added to assay plates containing compound.

Compounds were routinely dissolved in DMSO at a concentration of 12.8 mg/mL, with the exception of SPR741^{11,12,13} which was dissolved in water at a concentration of 5 mg/mL.

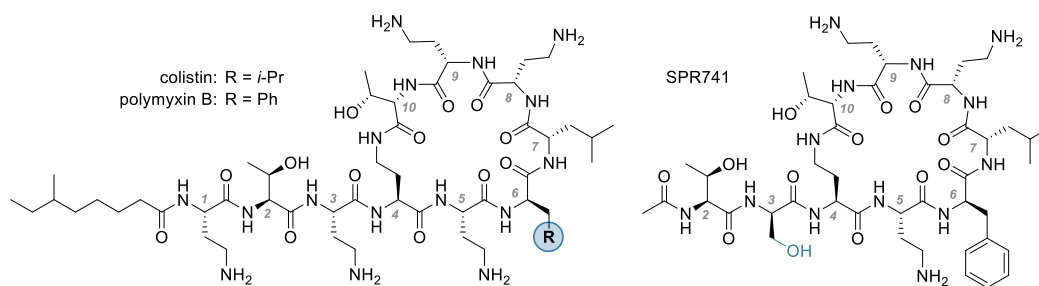


Figure S3. Structures of colistin, polymyxin B, and SPR741.

The minimum inhibitory concentrations (MICs) shown in Table 1 and Table 2 of the manuscript were determined by broth microdilution assay in 384-well plates for all compounds except **16** and **17** and performed in duplicate. Compounds were transferred to assay plates using an Echo Acoustic Dispenser (transfer volume: 2.5–780 nL; stock solutions 12.8 mg/mL). Growth was unperturbed with up to 2% [v/v] DMSO and backfilling plates was therefore deemed unnecessary. For the data presented in Table 3 and for compounds **16** and **17** in Table 1, a 2-fold dilution series of compound was added to each well of a 96-well plate prior to addition of bacteria. For checkerboard experiments, an 8×12 matrix of SPR741 and metergoline analogue (**15** or **38**) was created with two-fold serial dilutions of each compound, added to a 96-well plate prior to addition of bacteria. Assay plates were incubated for 16–20 h at 37 °C with shaking

11. Vaara, M.; Siikanen, O.; Apajalahti, J.; Fox, J.; Frimodt-Moller, N.; He, H.; Poudyal, A.; Li, J.; Nation, R. L.; Vaara, T. A novel polymyxin derivative that lacks the fatty acid tail and carries only three positive charges has strong synergism with agents excluded by the intact outer membrane. *Antimicrob. Agents Chemother.* **2010**, *54*, 3341–3346 (doi:10.1128/AAC.01439-09).
12. Zurawski, D. V.; Reinhart, A. A.; Alamneh, Y. A.; Pucci, M. J.; Abu-Taleb, R.; Shearer, J. P.; Demons, S. T.; Tyner, S. D.; Lister, T. SPR741, an antibiotic adjuvant, potentiates the *in vitro* and *in vivo* activity of rifampin against clinically relevant extensively drug-resistant *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2017**, *61*, e01239-17 (doi:10.1128/AAC.01239-17).
13. French, S.; Farha, M.; Ellis, M. J.; Sameer, Z.; Côté, J.-P.; Cotroneo, N.; Lister, T.; Rubio, A.; Brown, E. D. Potentiation of antibiotics against Gram-negative bacteria by polymyxin B analogue SPR741 from unique perturbation of the outer membrane. *ACS Infect. Dis.* **2020**, *6*, 1405–1412 (doi:10.1021/acsinfecdis.9b00159).

and optical density was measured with a Tecan M1000 Infinite Pro plate reader. The MIC was the concentration that inhibited growth >95% compared to the DMSO control.

MIC values obtained for **1–15** against *S. Tm* and MRSA using 384-well plate format generally correlate well with MICs reported previously³ using the 96-well format, with the exception of compound **15**, which shows MICs vs MRSA of 0.5 and 2.56 µg/mL, respectively. It is possible that the poor solubility of **15** following a freeze-thaw process is a contributing factor to the poorer MIC in 384-well format, which used the Echo dispenser for compound transfer.

Antimicrobial Disc Diffusion Assay

Overnight cultures were started from a single colony, and subcultured 1:100 in MHB for 1 hr at 37 °C with shaking. Cultures were diluted 10-fold in 20 mL MHB to approximately 1×10^6 CFU/mL and then poured onto 120 × 120 mm petri dishes containing MHB agar. The cell suspension was aspirated off the surface of the agar after 30 s, and plates were dried in a laminar flow hood for 10 min. Ten microlitres of compound stock solution dissolved in DMSO (5–100 µg per disc) was added to sterile discs (BH Taxo Blank Discs, ¼ inch diameter) prior to placing on top of the lawn of bacteria. Plates were incubated for 18 h at 37 °C prior to imaging. Discs for penicillin G, oxacillin, meropenem, ceftriaxone, azithromycin, tetracycline, and novobiocin contained 5 µg compound. Discs for vancomycin, gentamycin, and ciprofloxacin contained 10 µg compound. Discs for compounds **15** and **38** contained 20 µg compound. Discs for metergoline (**1**), **28**, and **44** contained 100 µg compound.

Animal Experiments

Experiments were conducted according to guidelines set by the Canadian Council on Animal Care, using protocols approved by the Animal Review Ethics Board at McMaster University under Animal Use Protocol #20-12-43. Before infection, mice were relocated at random from a housing cage to treatment or control cages. No animals were excluded from analyses, and blinding was considered unnecessary. Six- to eight-week-old BALB/c mice were pretreated with 150 mg/kg (day –4) and 100 mg/kg (day –1) of cyclophosphamide to render mice neutropenic. Mice were then anesthetized using isoflurane and administered the analgesic buprenorphine (0.1 mg/kg) subcutaneously. A 2-cm² abrasion on the dorsal surface of the mouse was inflicted through tape-stripping to the basal layer of epidermis using approximately 25–30 pieces of autoclave tape. Mice were infected with $\sim 10^6$ CFU *S. aureus* (USA300 JE2) directly pipetted on the wounded skin. The infection was established for 1 h prior to treatment with Glaxal Base supplemented with vehicle (2.5% DMSO) or **38** (0.1% w/v). Groups of mice were treated 1 h, 4 h, 8 h, 12 h, and 20 h post-infection. Mice were euthanized at the experimental endpoint of 24 h and the wounded tissue collected, homogenized, and plated onto LB to quantify bacterial load.

Glaxal Base (www.glaxalbase.ca/product/moisturizing-cream) supplemented with **38** was prepared at 0.1% (w/v), which is equivalent to 1 mg/mL and 2.13 mM. A total of 0.5 g (~ 0.55 mL) of **38**-supplemented Glaxal Base cream was used for each of the five mice, with application of 0.1 g cream by Q-tip cotton swab at each of the five time points (1 h, 4 h, 8 h, 12 h, and 20 h post-infection). A total of 0.55 mg of compound **38** (0.0012 mmol) was used for each mouse.

Synthetic Experimental Procedures

General

Chemical shifts in ^1H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with calibration to TMS (δ_{H} , δ_{C} 0.0) or the residual solvent peaks according to values reported by Gottlieb et al. (chloroform: δ_{H} 7.26, δ_{C} 77.16; acetone: δ_{H} 2.05, δ_{C} 29.84, 206.26; methanol: δ_{H} 3.31, δ_{C} 49.00; DMSO: δ_{H} 2.50, δ_{C} 39.52).¹⁴ When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sept., septet; dd, doublet of doublets; m, multiplet; br, broad; app., apparent; *gem*, geminal. ^1H NMR spectra were acquired at 600 or 700 MHz with a default digital resolution (Brüker parameter: FIDRES) of 0.18 and 0.15 Hz/point, respectively. Coupling constants reported herein therefore have uncertainties of ± 0.4 Hz and ± 0.3 Hz, respectively. All assignments of protons and carbons relied on data from 2-dimensional NMR experiments including COSY, HMQC, and HMBC. The ^{13}C NMR spectra provided herein ($^{13}\text{C}\{^1\text{H}\}$ DEPTQ-135; Brüker pulse program deptqgsp) show CH and CH₃ carbon signals below the baseline and C and CH₂ carbons above the baseline. Melting points (mp) are uncorrected. Reactions were carried out at room temperature (rt) if temperature is not specified. Compounds purified by normal-phase flash chromatography used Teledyne CombiFlash Rf+ and NextGen 300+ purification systems (www.teledyneisco.com) with pre-packed silica cartridges (either 40–63 μM or 20–40 μM particle size). High-resolution mass spectrometry (HRMS) data was obtained using a Brüker micrOTOF II system with electrospray ionization (ESI) and paired with an Agilent HPLC and UV detector.

Metergoline (5*R*,8*S*,10*R*, CAS# 17692-51-2), ClCO₂Et, AcCl, SOCl₂, BzCl, phenylacetyl chloride, pyridine, Et₃N, and *i*-Pr₂NEt were purchased from Sigma-Aldrich (www.sigmaaldrich.com). Boc₂O, phenoxyacetic acid, *N*-phenylglycine, HOBT, hydrocinnamic acids (2-OMe, 4-Cl, 3-Cl, 2-F, 4-F, 2-Br, 4-Br), cinnamic acids **54e**, **54g**, **54i**, and **54l**, aldehydes **52j**, **52m**, and **52p**, and acetophenones **52t** and **52v** were purchased from Oakwood Chemical (Estill, South Carolina, www.oakwoodchemical.com). Benzyl isocyanate (BnNCO), 10% Pd/C, EDC·HCl, triethyl phosphonoacetate, trimethyl phosphonoacetate, cinnamic acids **54a**, **54c**, **54d**, **54h**, and **54o**, aldehydes **52k**, **52m**, **52q**, **52r**, and **52s**, and ketone **52w** were purchased from AK Scientific, Inc. (Union City, California, www.aksci.com). 3-Trifluoromethylcinnamic acid **54f** was purchased from Enamine (Kyiv, Ukraine, www.enaminestore.com). CH₂Cl₂, EtOAc, MeOH, hexanes, THF, NaOH, LiOH, cinnamic acid **54b**, and ketone **52u** were purchased from Fisher Scientific (www.fishersci.ca).

All samples of synthetic compounds used for assay were judged to be >90% pure NMR.

General Procedure A

To a solution of amine **2** (1.0 equiv), EDC·HCl (1.2 equiv), HOBT (1.2 equiv), and a carboxylic acid **54** (1.2 equiv) in CH₂Cl₂ (0.02 M) was added *i*-Pr₂NEt (3 equiv). The reaction mixture was stirred at rt for 3–24 h and the progress of the reaction followed by thin-layer chromatography (TLC). Upon completion, the reaction mixture was diluted with CH₂Cl₂, washed with saturated aqueous Na₂CO₃, dried over Na₂SO₄, and concentrated under reduced pressure. Products were purified by flash chromatography

14. Gottlieb, H. G.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512–7515 (doi:10.1021/jo971176v).

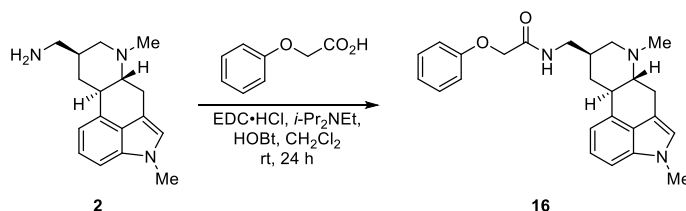
(MeOH/CH₂Cl₂) on silica gel. *i*-Pr₂NEt was not used in all EDC coupling reactions but seemed to improve solubility and reaction rate. Metergoline analogues were often isolated as viscous oils when concentrated from CH₂Cl₂/MeOH, but solidification could often be induced by taking up the oil in CH₂Cl₂ (~0.5–1 mL), adding Et₂O or EtOAc (5–10 mL), and then concentrating by rotary evaporation.

General Procedure B

Some acrylic acids **54** were converted to their corresponding acid chlorides **55** in order to acylate amine **2**. Thionyl chloride (SOCl₂, 2 mL) was added to a solution of acrylic acid **54** (0.25 mmol) in CH₂Cl₂ (3 mL) and heated to reflux for 6–24 h. The reaction mixture was concentrated in vacuo and the resulting crude acid chloride used without characterization in the following reaction with amine **2**.

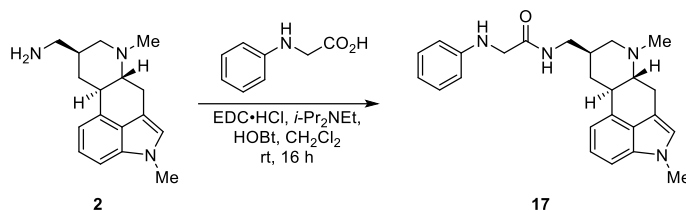
The appropriate acid chloride **55** (1.1–1.2 equiv) was combined with amine **2** (30 mg, 1.0 equiv) and stirred in CH₂Cl₂ (5 mL) at rt for 6–24 h. The progress of the reaction was followed by thin-layer chromatography (TLC). Upon completion, the reaction mixture was diluted with CH₂Cl₂, washed with saturated aqueous Na₂CO₃, dried over Na₂SO₄, and concentrated under reduced pressure. Products were purified by flash chromatography (MeOH/CH₂Cl₂) on silica gel.

N-(3-Phenoxyacetyl) ergoline derivative (**16**)



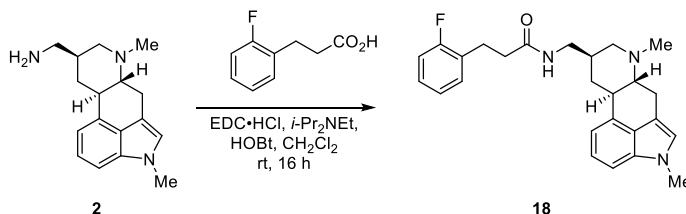
According to General Procedure A, *i*-Pr₂NEt (150 μ L, 0.86 mmol) was added to a solution of amine **2** (77 mg, 0.29 mmol), EDC·HCl (66 mg, 0.34 mmol), HOBT (46 mg, 0.34 mmol), and phenoxyacetic acid (52 mg, 0.34 mmol) in CH₂Cl₂ (6 mL). After stirring the reaction mixture overnight at rt for 24 h, it was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/CH₂Cl₂) provided an oily residue that was resuspended in ~5:1 Et₂O/CH₂Cl₂ (5 mL) and concentrated in vacuo to furnish the amide **16** as an off-white solid (105 mg, 0.26 mmol, 91%). *R*_f = 0.40 (7.5% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.33 (dd, *J* = 7.4, 8.1 Hz, 2H), 7.18 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 6.71 (brs, 1H), 4.55 (s, 2H), 3.75 (s, 3H), 3.43–1.31 (m, 3H), 3.05–2.97 (m, 2H), 2.73 (brt, *J* = 12.5 Hz, 1H), 2.64 (brd, *J* = 12.5 Hz, 1H), 2.48 (s, 3H), 2.25–2.16 (m, 2H), 2.01 (t, *J* = 11.4 Hz, 1H), 1.17 (q, *J* = 12.5 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 168.6, 157.3, 134.5, 133.0, 130.0 (2C), 126.5, 122.8, 122.7, 122.3, 114.8 (2C), 112.7, 110.4, 107.0, 67.5, 67.4, 61.3, 43.2, 42.8, 40.4, 36.4, 32.9, 32.0, 26.9. LCMS (ESI) *m/z*: 404.2333 calcd for C₂₅H₃₀N₃O₂⁺ [*M* + *H*]⁺; Found 404.2330.

N-(*N*-Phenylglyciny) ergoline derivative (**17**)



According to General Procedure A, *i*-Pr₂NEt (195 μ L, 1.11 mmol) was added to a solution of amine **2** (100 mg, 0.37 mmol), EDC·HCl (85 mg, 0.44 mmol), HOBT (60 mg, 0.44 mmol), and *N*-phenylglycine (67 mg, 0.44 mmol) in CH₂Cl₂ (7.5 mL). After stirring the reaction mixture overnight at rt for 24 h, it was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/CH₂Cl₂) provided amide **17** as an off-white amorphous solid (142 mg, 0.35 mmol, 95%). *R*_f = 0.29 (7.5% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.20 (dd, *J* = 6.9, 7.9 Hz, 2H), 7.16 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.02 (brs, 1H), 6.81–6.76 (m, 2H), 6.72 (s, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 4.43 (brs, 1H), 3.83 (d, *J* = 3.9 Hz, 2H), 3.74 (s, 3H), 3.37 (brd, *J* = 14.5 Hz, 1H), 3.34–3.29 (m, 1H), 3.28–3.21 (m, 1H), 3.16–3.05 (m, 2H), 2.91–2.81 (m, 1H), 2.58 (brd, *J* = 12.5 Hz, 1H), 2.53 (s, 3H), 2.38–2.21 (m, 2H), 2.15–2.07 (m, 1H), 1.12 (q, *J* = 12.1 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 171.1, 147.2, 134.5, 132.1, 129.6 (2C), 126.3, 122.9, 122.8, 119.3, 113.4 (2C), 112.9, 109.6, 107.2, 67.5, 60.9, 48.8, 42.7, 42.6, 39.7, 35.8, 32.9, 31.7, 26.3. LCMS (ESI) *m/z*: 403.2492 calcd for C₂₅H₃₁N₄O⁺ [M + H]⁺; Found 403.2506.

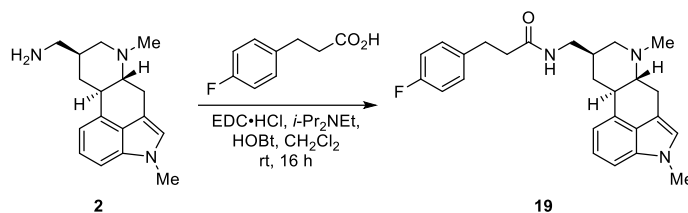
N-(2-Fluoro-hydrocinnamoyl) ergoline derivative (**18**)



According to General Procedure A, *i*-Pr₂NEt (78 μ L, 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(2-fluorophenyl)propanoic acid (30 mg, 0.17 mmol) in CH₂Cl₂ (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH₂Cl₂ (50 mL), washed with saturated Na₂CO₃ (2 \times 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/CH₂Cl₂) provided amide **18** as an off-white oily solid (12 mg, 0.029 mmol, 19%). ¹H NMR (600 MHz, CDCl₃): δ 7.24 (ddd, *J* = 7.5, 1.6 Hz, ⁴*J*_{HF} = 6.9 Hz, 1H), 7.18 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.15 (td, *J* = 7.5, 1.6 Hz, ⁴*J*_{HF} = 5.7 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (ddd, *J* = 7.5, 1.0 Hz, ³*J*_{HF} = 8.9 Hz, 1H), 6.84 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 5.79 (brs, 1H), 3.75 (s, 3H), 3.37 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.29 (dt, *J* = 7.2, 14.1 Hz, 1H), 3.20–3.14 (m, 1H), 3.02 (t, *J* = 7.5 Hz, 2H), 3.05–2.97 (m, 2H), 2.75 (brt, *J* = 10.6, 14.6 Hz, 1H), 2.58–2.51 (m, 4H), 2.49 (s, 3H), 2.23 (td, *J* = 10.6, 4.3 Hz, 1H), 2.16–2.07 (brs, 1H), 2.00 (t, *J* = 11.4 Hz, 1H), 1.12 (q, *J* = 12.3 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 172.1, 161.1 (¹*J*_{C,F} = 245 Hz), 134.3, 132.6, 130.9 (³*J*_{C,F} = 5.1 Hz), 128.1 (³*J*_{C,F} = 8.1 Hz), 127.6 (²*J*_{C,F} = 16.3 Hz), 126.3, 124.2 (⁴*J*_{C,F} = 4.1 Hz), 122.7, 122.6, 115.3 (²*J*_{C,F} = 21.4 Hz), 112.6, 110.0,

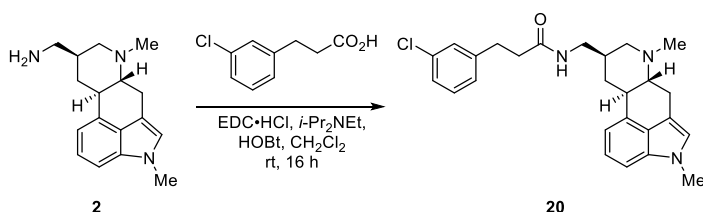
107.0, 67.3, 61.0, 43.1, 42.9, 40.0, 36.8, 36.0, 32.8, 31.8, 26.5, 25.4. ^{19}F NMR (188 MHz, CDCl_3): δ – 117.2. LCMS (ESI) m/z : 420.2446 calcd for $\text{C}_{26}\text{H}_{31}\text{FN}_3\text{O}^+ [\text{M} + \text{H}]^+$; Found 420.2452.

N-(4-Fluoro-hydrocinnamoyl) ergoline derivative (**19**)



According to General Procedure A, *i*-Pr₂NEt (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(4-fluorophenyl)propanoic acid (30 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to give an off-white solid. Flash chromatography (0 \rightarrow 15% MeOH/ CH_2Cl_2) provided amide **19** as an off-white amorphous solid (43 mg, 0.10 mmol, 69%). ^1H NMR (600 MHz, CDCl_3): δ 7.21–7.15 (m, 3H), 7.12 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 8.6 Hz, $^3J_{\text{HF}}$ = 8.6 Hz, 2H), 6.84 (d, J = 7.1 Hz, 1H), 6.73 (s, 1H), 5.65 (brs, 1H), 3.75 (s, 3H), 3.37 (dd, J = 14.6, 4.3 Hz, 1H), 3.28 (dt, J = 7.2, 14.0 Hz, 1H), 3.22–3.16 (m, 1H), 3.05–2.98 (m, 2H), 2.96 (t, J = 7.3 Hz, 2H), 2.75 (brt, J = 10.6, 14.6 Hz, 1H), 2.58 (brd, J = 12.8 Hz, 1H), 2.52–2.47 (m, 2H), 2.49 (s, 3H), 2.21 (td, J = 10.6, 4.2 Hz, 1H), 2.16–2.08 (brs, 1H), 1.98 (t, J = 11.4 Hz, 1H), 1.12 (q, J = 12.3 Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 172.0, 161.4 ($^1J_{\text{C,F}}$ = 244 Hz), 136.5 ($^4J_{\text{C,F}}$ = 3.0 Hz), 134.4, 132.6, 129.8 ($^3J_{\text{C,F}}$ = 7.8 Hz, 2C), 126.3, 122.7, 122.6, 115.3 ($^2J_{\text{C,F}}$ = 21.2 Hz, 2C), 112.6, 110.0, 107.0, 67.4, 61.0, 43.1, 42.9, 40.1, 38.5, 36.1, 32.8, 31.8, 30.8, 26.6. ^{19}F NMR (188 MHz, CDCl_3): –115.5. LCMS (ESI) m/z : 420.2446 calcd for $\text{C}_{26}\text{H}_{31}\text{FN}_3\text{O}^+ [\text{M} + \text{H}]^+$; Found 420.2459.

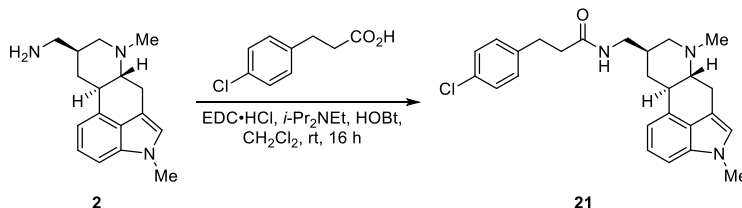
N-(3-Chloro-hydrocinnamoyl) ergoline derivative (**20**)



According to General Procedure A, *i*-Pr₂NEt (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(3-chlorophenyl)propanoic acid (31 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to give an off-white solid. Flash chromatography (0 \rightarrow 15% MeOH/ CH_2Cl_2) provided amide **20** as a pale yellow oily solid (10 mg, 0.024 mmol, 16%). ^1H NMR (600 MHz, CDCl_3): δ 7.21 (brs, 1H), 7.20–7.15 (m, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 6.83 (d, J = 7.1 Hz, 1H), 6.72 (s, 1H), 5.85 (brs, 1H), 3.74 (s, 3H), 3.36 (dd, J = 14.6, 4.3 Hz, 1H), 3.28 (dt, J = 7.0, 14.0 Hz, 1H), 3.17 (dt, J = 5.5, 14.0 Hz,

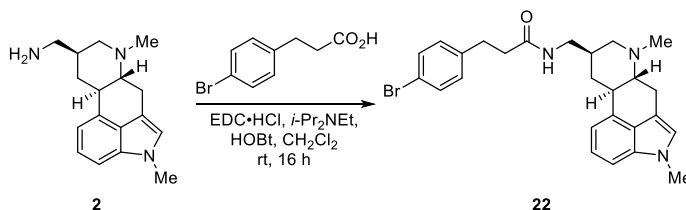
1H), 3.01–2.94 (m, 4H), 2.74 (brt, $J = 11.0, 14.6$ Hz, 1H), 2.55 (brd, $J = 12.3$ Hz, 1H), 2.50 (dt, $J = 7.5, 3.5$ Hz, 2H), 2.48 (s, 3H), 2.21 (td, $J = 10.7, 4.3$ Hz, 1H), 2.15–2.07 (brs, 1H), 1.97 (t, $J = 11.4$ Hz, 1H), 1.09 (q, $J = 12.3$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 171.9, 142.9, 134.3, 134.2, 132.6, 129.8, 128.5, 126.7, 126.5, 126.3, 122.7, 122.5, 112.6, 110.0, 107.0, 67.3, 61.0, 43.1, 42.9, 40.0, 38.0, 36.0, 32.8, 31.8, 31.3, 26.5. LCMS (ESI) m/z : 436.2150 calcd for $\text{C}_{26}\text{H}_{31}\text{Cl}^{35}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$; Found 436.2151.

N-(4-Chloro-hydrocinnamoyl) ergoline derivative (**21**)



According to General Procedure A, $i\text{-Pr}_2\text{NEt}$ (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(4-chlorophenyl)propanoic acid (31 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) provided amide **21** as a pale yellow oily solid (31 mg, 0.071 mmol, 48%). ^1H NMR (600 MHz, CDCl_3): δ 7.23 (d, $J = 8.4$ Hz, 2H), 7.18 (dd, $J = 7.1, 8.2$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 7.1$ Hz, 1H), 6.72 (s, 1H), 5.80–5.74 (brs, 1H), 3.74 (s, 3H), 3.36 (dd, $J = 14.6, 4.4$ Hz, 1H), 3.25 (dt, $J = 7.2, 14.0$ Hz, 1H), 3.21–3.15 (m, 1H), 3.00–2.92 (m, 4H), 2.72 (brt, $J = 11.0, 14.6$ Hz, 1H), 2.57 (brd, $J = 10.7$ Hz, 1H), 2.49 (t, $J = 5.6$ Hz, 2H), 2.46 (s, 3H), 2.18 (td, $J = 4.4, 11.0$ Hz, 1H), 2.13–2.05 (m, 1H), 1.93 (t, $J = 11.4$ Hz, 1H), 1.11 (q, $J = 12.3$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 171.91, 139.3, 134.3, 132.7, 132.0, 129.8 (2C), 128.6 (2C), 126.3, 122.7, 122.6, 112.5, 110.1, 106.9, 67.3, 61.1, 43.1, 43.0, 40.2, 38.2, 36.2, 32.8, 31.9, 31.0, 26.6. LCMS (ESI) m/z : 436.2150 calcd for $\text{C}_{26}\text{H}_{31}\text{Cl}^{35}\text{N}_3\text{O}^+ [\text{M} + \text{H}]^+$; Found 436.2144.

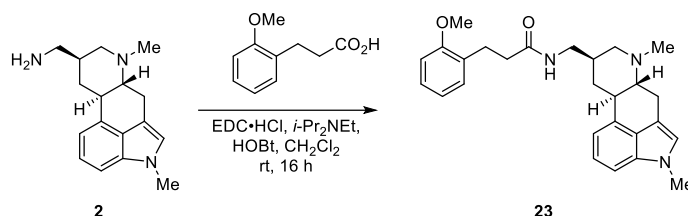
N-(4-Bromo-hydrocinnamoyl) ergoline derivative (**22**)



According to General Procedure A, $i\text{-Pr}_2\text{NEt}$ (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(4-bromophenyl)propanoic acid (39 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) provided amide **22** as a pale yellow oily solid (45 mg, 0.094 mmol, 63%). ^1H NMR (600 MHz, CDCl_3): δ 7.38 (d, $J = 7.2$ Hz, 2H), 7.21–7.15 (m, 1H), 7.14–7.03 (m, 3H), 6.84 (d, $J = 6.1$ Hz, 1H),

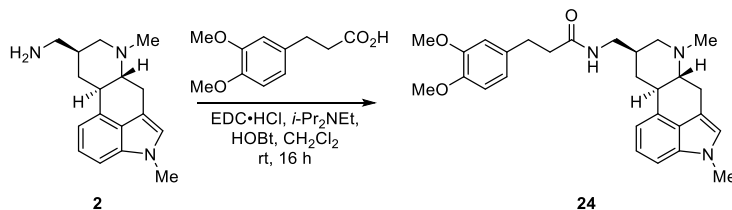
6.72 (s, 1H), 5.74 (brs, 1H), 3.74 (s, 3H), 3.36 (dd, $J = 14.6, 4.4$ Hz, 1H), 3.26 (m, 1H), 3.21–3.15 (m, 1H), 3.00–2.92 (m, 4H), 2.76–2.64 (m, 1H), 2.57 (brd, $J = 10.7$ Hz, 1H), 2.53–2.43 (m, 2H), 2.46 (s, 3H), 2.23–2.14 (m, 1H), 2.13–2.05 (m, 1H), 1.93 (t, $J = 10.9$ Hz, 1H), 1.10 (q, $J = 12.0$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 171.9, 139.8, 134.3, 132.7, 131.6 (2C), 130.2 (2C), 126.4, 122.7, 122.6, 120.0, 112.5, 110.2, 106.9, 67.3, 61.1, 43.1, 43.0, 40.2, 38.1, 36.2, 32.8, 31.9, 31.0, 26.6. LCMS (ESI) m/z : 480.1645 calcd for $\text{C}_{26}\text{H}_{31}\text{Br}^{79}\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 480.1648.

***N*-(2-Methoxy-hydrocinnamoyl) ergoline derivative (23)**



According to General Procedure A, *i*-Pr₂NEt (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(2-methoxyphenyl)propanoic acid (31 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/ CH_2Cl_2) provided amide **23** as a pale yellow oily solid (27 mg, 0.063 mmol, 42%). ^1H NMR (600 MHz, CDCl_3): 7.19–7.13 (m, 3H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 6.85–6.81 (m, 2H), 6.71 (s, 1H), 5.95 (brs, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.35 (dd, $J = 14.5, 4.3$ Hz, 1H), 3.25 (dt, $J = 7.1, 14.0$ Hz, 1H), 3.19–3.13 (m, 1H), 3.03–2.94 (m, 4H), 2.75 (dd, $J = 11.0, 14.6$ Hz, 1H), 2.56–2.52 (m, 1H), 2.52 (t, $J = 7.6$ Hz, 2H), 2.48 (s, 3H), 2.21 (td, $J = 4.3, 10.6$ Hz, 1H), 2.15–2.06 (m, 1H), 1.97 (t, $J = 11.5$ Hz, 1H), 1.08 (q, $J = 12.3$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): 173.0, 157.3, 134.3, 132.5, 130.1, 129.0, 127.6, 126.3, 122.7, 122.6, 120.6, 112.7, 110.3, 109.9, 107.0, 67.3, 61.0, 55.3, 43.0, 42.8, 40.0, 36.7, 36.0, 32.8, 31.8, 26.6, 26.4. LCMS (ESI) m/z : 432.2646 calcd for $\text{C}_{27}\text{H}_{34}\text{N}_3\text{O}_2^+$ $[\text{M} + \text{H}]^+$; Found 432.2657.

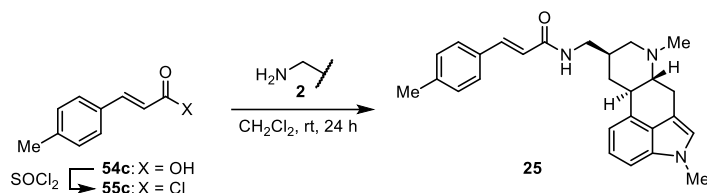
***N*-(3,4-Dimethoxy-hydrocinnamoyl) ergoline derivative (24)**



According to General Procedure A, *i*-Pr₂NEt (78 μL , 0.49 mmol) was added to a solution of amine **2** (40 mg, 0.15 mmol), EDC·HCl (34 mg, 0.18 mmol), HOBT (24 mg, 0.18 mmol), and 3-(3,4-dimethoxyphenyl)propanoic acid (37 mg, 0.18 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/ CH_2Cl_2) provided amide **24** as a pale yellow oily solid (34 mg, 0.074 mmol, 50%). ^1H NMR (600

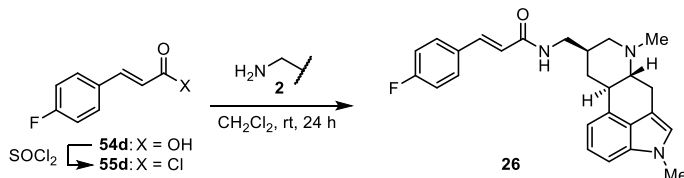
MHz, CDCl₃): 7.16 (dd, $J = 8.2, 7.1$ Hz, 1H), 7.09 (d, $J = 8.2$ Hz, 1H), 6.83 (d, $J = 7.1$ Hz, 1H), 6.77–6.73 (m, 3H), 6.71 (s, 1H), 6.05 (brs, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.34 (dd, $J = 14.6, 4.3$ Hz, 1H), 3.25 (dt, $J = 6.1, 12.2$ Hz, 1H), 3.20–3.13 (m, 1H), 3.02–2.95 (m, 2H), 2.93 (t, $J = 7.6$ Hz, 2H), 2.73 (brt, $J = 11.0, 14.6$ Hz, 1H), 2.56 (brd, $J = 12.6$ Hz, 1H), 2.51 (t, $J = 7.6$ Hz, 2H), 2.46 (s, 3H), 2.19 (td, $J = 4.3, 10.7$ Hz, 1H), 2.15–2.07 (m, 1H), 1.94 (t, $J = 11.5$ Hz, 1H), 1.08 (q, $J = 12.4$ Hz, 1H). ¹³C NMR (150 MHz, CDCl₃): 171.5, 148.8, 147.4, 134.3, 133.4, 132.5, 126.3, 122.7, 122.6, 120.1, 112.6, 111.8, 111.3, 109.9, 107.0, 67.3, 61.0, 55.8, 55.7, 43.0, 42.8, 40.0, 38.5, 35.9, 32.8, 31.7, 31.3, 26.4. LCMS (ESI) m/z : 462.2751 calcd for C₂₈H₃₆N₃O₃⁺ [M + H]⁺; Found 462.2753.

N-(4-Methyl-*trans*-cinnamoyl) ergoline derivative (25)



SOCl₂ (3 mL) was added to a solution of 3-(4-methylphenyl)-2-propenoic acid **54c** (25.4 mg, 0.15 mmol) in CH₂Cl₂ (3 mL) and heated to reflux for 6 h. The solution was then cooled to rt and concentrated in vacuo. The crude acid chloride **55c** (26.6 mg, 0.15 mmol) and amine **2** (34.3 mg, 0.13 mmol) were dissolved in CH₂Cl₂ and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂, washed with satd Na₂CO₃ (50 mL), and brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **25** as an off-white solid (35 mg, 0.0845 mmol 66%). $R_f = 0.60$ (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.63 (d, $J = 15.6$, 1H), 7.42 (d, $J = 7.8$ Hz, 2H), 7.21–7.16 (m, 3H), 7.12 (d, $J = 8.2$ Hz, 1H), 6.90 (d, $J = 7.0$ Hz, 1H), 6.73 (s, 1H), 6.40 (d, $J = 15.6$ Hz, 1H), 5.83 (brs, 1H), 3.75 (s, 3H), 3.46 (dt, $J = 14.0, 7.1$ Hz, 1H), 3.43–3.36 (m, 2H), 3.16 (brd, $J = 10.8$ Hz, 1H), 3.06 (brt, $J = 9.4$ Hz, 1H), 2.76 (brt, $J = 12.8$ Hz, 1H), 2.71 (d, $J = 12.7$ Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H), 2.29–2.21 (m, 2H), 2.11 (t, $J = 11.3$ Hz, 1H), 1.23 (q, $J = 12.4$ Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 166.5, 141.3, 140.1, 134.5, 132.9, 132.2, 129.7 (2C), 128.0 (2C), 126.5, 122.9, 122.8, 119.7, 112.8, 110.3, 107.1, 67.5, 61.4, 43.5, 43.2, 40.4, 36.6, 32.9, 32.2, 29.9, 26.8, 21.6. LCMS (ESI) m/z : 414.2540 calcd for C₂₇H₃₂N₃O⁺ [M + H]⁺; Found 414.2542.

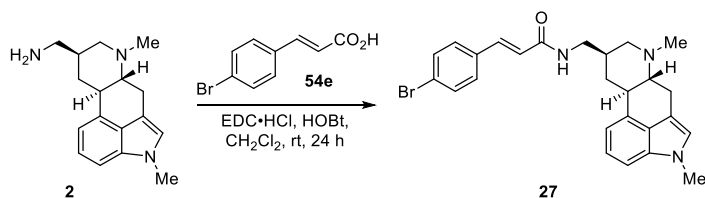
N-(4-Fluoro-*trans*-cinnamoyl) ergoline derivative (26)



SOCl₂ (3 mL) was added to a solution of 3-(4-fluorophenyl)-2-propenoic acid **54d** (25.4 mg, 0.15 mmol) in CH₂Cl₂ (3 mL) and heated to reflux for 6 h. The solution was then cooled to rt and concentrated in vacuo. The crude acid chloride **55d** (28.1 mg) was combined with amine **2** (37.1 mg, 0.14 mmol) in CH₂Cl₂ and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂, washed with satd Na₂CO₃

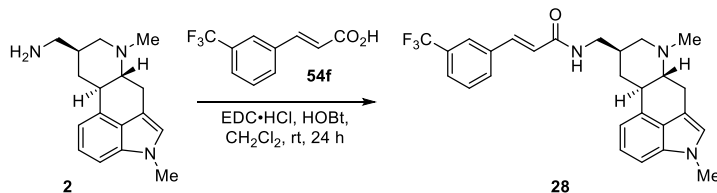
(50 mL) and brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide the *p*-fluoro cinnamide **26** (30.9 mg, 0.074 mmol, 48%) as an oily solid. *R*_f = 0.45 (10% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.47 (dd, *J* = 8.6 Hz, ⁴*J*_{H,F} = 5.5 Hz, 2H), 7.17 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 8.6 Hz, ³*J*_{H,F} = 8.6 Hz, 2H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.72 (s, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.11 (brs, 1H), 3.74 (s, 3H), 3.46–3.35 (m, 3H), 3.12 (brd, *J* = 11.4 Hz, 1H), 3.01 (td, *J* = 12.6, 3.4 Hz, 1H), 2.75–2.67 (m, 2H), 2.49 (s, 3H), 2.26–2.16 (m, 2H), 2.06 (t, *J* = 11.4 Hz, 1H), 1.20 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 166.2, 163.6 (¹*J*_{C,F} = 250 Hz), 140.0, 134.5, 133.0, 131.2 (⁴*J*_{C,F} = 3.3 Hz), 129.7 (³*J*_{C,F} = 8.2 Hz, 2C), 126.5, 122.8, 122.7, 120.5, 116.0 (²*J*_{C,F} = 21.7 Hz, 2C), 112.7, 110.4, 107.2, 67.4, 61.4, 43.5, 43.2, 40.4, 36.6, 32.9, 32.1, 26.8. LCMS (ESI) *m/z*: 418.2289 calcd for C₂₆H₂₉FN₃O⁺ [*M* + *H*]⁺; Found 418.2290.

N-(4-Bromo-*trans*-cinnamoyl) ergoline derivative (**27**)



As a modification of General Procedure A, amine **2** (40 mg, 0.15 mmol) was combined with EDC·HCl (29 mg, 0.15 mmol), HOBT (23 mg, 0.15 mmol), and 4-bromocinnamic acid **54e** (27 mg, 0.12 mmol) in CH₂Cl₂ (5 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide the *p*-bromo cinnamide **27** as an off-white amorphous solid (14 mg, 0.030 mmol, 25%). *R*_f = 0.58 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.59 (d, *J* = 15.6 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.18 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 5.83 (brs, 1H), 3.76 (s, 3H), 3.46 (ddd, *J* = 14.0, 7.6, 6.5 Hz, 1H), 3.43–3.37 (m, 2H), 3.12 (brd, *J* = 11.4 Hz, 1H), 3.06–3.00 (m, 1H), 2.77–2.68 (m, 2H), 2.51 (s, 3H), 2.27–2.20 (m, 2H), 2.09 (t, *J* = 11.4 Hz, 1H), 1.23 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 165.9, 140.2, 134.5, 133.9, 133.0, 132.2 (2C), 129.4 (2C), 126.5, 124.0, 122.9, 122.8, 121.3, 112.7, 110.4, 107.1, 67.6, 61.5, 43.6, 43.3, 40.5, 36.7, 32.9, 32.2, 26.9. LCMS (ESI) *m/z*: 478.1489 calcd for C₂₆H₂₉⁷⁹BrN₃O⁺ [*M* + *H*]⁺; Found 478.1478.

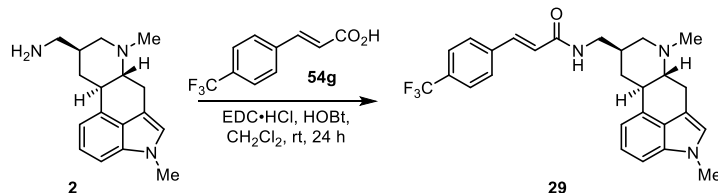
N-(3-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**28**)



As a modification of General Procedure A, amine **2** (49 mg, 0.18 mmol) was combined with EDC·HCl (35 mg, 0.18 mmol), HOBT (28 mg, 0.18 mmol), and 3-trifluoromethylcinnamic acid **54f** (31 mg, 0.15

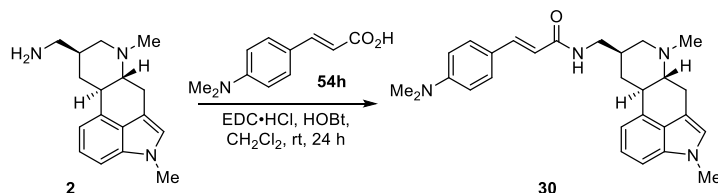
mmol) in CH₂Cl₂ (5 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide the *m*-CF₃ cinnamide **28** as an off-white amorphous solid (47 mg, 0.10 mmol, 70%). *R*_f = 0.60 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.78 (s, 1H), 7.71–7.64 (m, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 5.80 (brs, 1H), 3.76 (s, 3H), 3.46 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.43 (dd, *J* = 13.9, 6.6 Hz, 1H), 3.39 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.08 (brd, *J* = 11.2 Hz, 1H), 2.99 (brt, *J* = 11.2 Hz, 1H), 2.74–2.65 (m, 2H), 2.48 (s, 3H), 2.23–2.14 (m, 2H), 2.04 (t, *J* = 11.3 Hz, 1H), 1.22 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 165.5, 139.8, 135.8, 134.5, 133.3, 131.5 (q, ²*J*_{C,F} = 32.5 Hz), 131.4, 129.5, 126.6, 126.2 (q, ³*J*_{C,F} = 3.8 Hz), 124.1 (q, ³*J*_{C,F} = 3.6 Hz), 124.0 (q, ¹*J*_{C,F} = 272 Hz), 122.9, 122.7, 121.7, 112.7, 110.7, 107.0, 67.5, 61.6, 43.7, 43.5, 40.7, 36.9, 32.9, 32.3, 27.1. LCMS (ESI) *m/z*: 468.2257 calcd for C₂₇H₂₉F₃N₃O⁺ [M + H]⁺; Found 468.2253.

N-(4-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**29**)



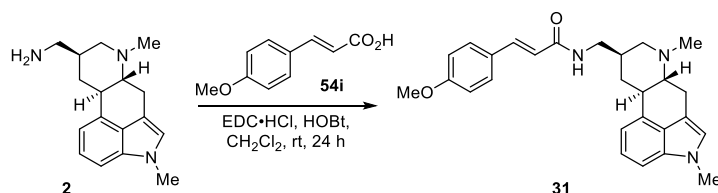
As a modification of General Procedure A, amine **2** (100 mg, 0.37 mmol) was combined with EDC·HCl (90 mg, 0.47 mmol), HOBT (71 mg, 0.47 mmol), and 3-trifluoromethylcinnamic acid **54g** (101 mg, 0.47 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide the *p*-CF₃ cinnamide **29** as an off-white amorphous solid (47 mg, 0.10 mmol, 70%). *R*_f = 0.58 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.68 (d, *J* = 15.6 Hz, 1H), 7.65–7.59 (m, 4H), 7.18 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 5.81 (brs, 1H), 3.76 (s, 3H), 3.46 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.43 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.39 (dd, *J* = 14.7, 4.2 Hz, 1H), 3.10 (brd, *J* = 10.7 Hz, 1H), 2.99 (brt, *J* = 10.4 Hz, 1H), 2.75–2.67 (m, 2H), 2.49 (s, 3H), 2.25–2.15 (m, 2H), 2.06 (t, *J* = 11.3 Hz, 1H), 1.23 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 165.5, 139.8, 138.4, 134.5, 133.2, 131.4 (q, ²*J*_{C,F} = 32.1 Hz), 128.1 (2C), 126.6, 125.9 (q, ³*J*_{C,F} = 3.8 Hz, 2C), 124.0 (q, ¹*J*_{C,F} = 272 Hz), 123.1, 122.9, 122.7, 121.7, 112.7, 110.6, 107.0, 67.5, 61.6, 43.7, 43.4, 40.6, 36.9, 32.9, 32.3, 27.0. LCMS (ESI) *m/z*: 468.2257 calcd for C₂₇H₂₉F₃N₃O⁺ [M + H]⁺; Found 468.2274.

N-(4-Dimethylamino-*trans*-cinnamoyl) ergoline derivative (**30**)



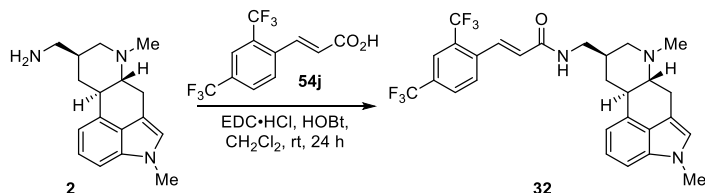
As a modification of General Procedure A, amine **2** (43 mg, 0.16 mmol) was combined with EDC·HCl (38 mg, 0.19 mmol), HOBT (32 mg, 0.21 mmol), and 4-dimethylaminocinnamic acid **54h** (38 mg, 0.20 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide the *p*-dimethylamino cinnamide **30** as an off-white amorphous solid (57 mg, 0.13 mmol, 81%). *R*_f = 0.63 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.58 (d, *J* = 15.5 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.71 (brs, 1H), 3.75 (s, 3H), 3.45 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.42–3.36 (m, 2H), 3.15 (brd, *J* = 10.5 Hz, 1H), 3.04 (brt, *J* = 10.1 Hz, 1H), 3.00 (s, 6H), 2.75–2.68 (m, 2H), 2.51 (s, 3H), 2.26–2.19 (m, 2H), 2.09 (t, *J* = 11.4 Hz, 1H), 1.23 (q, *J* = 12.5 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 167.2, 151.5, 141.6, 134.5, 133.1, 129.5 (2C), 126.6, 122.9, 122.8, 122.7, 115.5, 112.8, 112.1 (2C), 110.5, 107.0, 67.5, 61.5, 43.4, 43.2, 40.5, 40.4 (2C), 36.7, 32.9, 32.2, 26.8. LCMS (ESI) *m/z*: 443.2805 calcd for C₂₈H₃₅N₄O⁺ [M + H]⁺; Found 443.2824.

N-(4-Methoxy-*trans*-cinnamoyl) ergoline derivative (**31**)



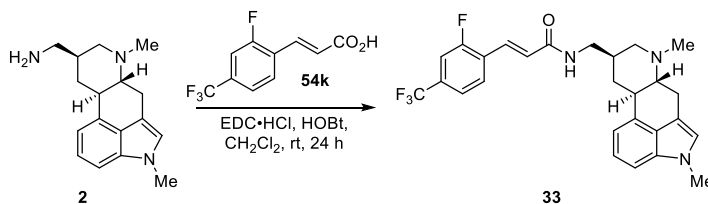
As a modification of General Procedure A, amine **2** (42 mg, 0.16 mmol) was combined with EDC·HCl (38 mg, 0.20 mmol), HOBT (33 mg, 0.21 mmol), and 4-methoxycinnamic acid **54i** (36 mg, 0.20 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (5→20% MeOH/CH₂Cl₂) provided the *p*-methoxy cinnamide **31** as an oily solid (59 mg, 0.14 mmol, 88%). *R*_f = 0.59 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.61 (d, *J* = 15.5 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.18 (dd, *J* = 7.1, 8.1 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.92–6.87 (m, 3H), 6.73 (s, 1H), 6.31 (d, *J* = 15.5 Hz, 1H), 5.80 (brs, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.45 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.42–3.36 (m, 2H), 3.12 (brd, *J* = 11.4 Hz, 1H), 3.01 (td, *J* = 11.1, 3.8 Hz, 1H), 2.75–2.68 (m, 2H), 2.50 (s, 3H), 2.24–2.18 (m, 2H), 2.07 (t, *J* = 11.4 Hz, 1H), 1.22 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 167.2, 151.5, 141.6, 134.5, 133.1, 129.5 (2C), 126.6, 122.9, 122.8, 122.7, 115.5, 112.8, 112.1 (2C), 110.5, 107.0, 67.5, 61.5, 43.4, 43.2, 40.5, 40.4 (2C), 36.7, 32.9, 32.2, 26.8. LCMS (ESI) *m/z*: 430.2489 calcd for C₂₇H₃₂N₃O₂⁺ [M + H]⁺; Found 430.2510.

N-(2,4-Di(trifluoro-*trans*-methyl)-cinnamoyl) ergoline derivative (**32**)



As a modification of General Procedure A, amine **2** (32 mg, 0.11 mmol) was combined with EDC·HCl (27 mg, 0.14 mmol), HOBT (22 mg, 0.14 mmol), and 2,4-di(trifluoromethyl)cinnamic acid **54j** (41 mg, 0.14 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **32** as an oily solid (67 mg, 0.13 mmol, 91%). *R*_f = 0.60 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.98 (d, *J* = 15.4 Hz, 1H), 7.93 (s, 1H), 7.80–7.75 (m, 2H), 7.18 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 6.51 (d, *J* = 15.4 Hz, 1H), 6.13 (brs, 1H), 3.75 (s, 3H), 3.48–3.40 (m, 1H), 3.39 (dd, *J* = 14.7, 4.3 Hz, 2H), 3.15 (brd, *J* = 11.0 Hz, 1H), 3.04 (td, *J* = 10.4, 3.4 Hz, 1H), 2.78–2.62 (m, 2H), 2.52 (s, 3H), 2.30–2.21 (m, 2H), 2.10 (t, *J* = 11.4 Hz, 1H), 1.23 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 164.8, 138.0, 135.5, 134.5, 132.8, 131.2 (q, ²*J*_{C,F} = 33.7 Hz), 129.6 (q, ²*J*_{C,F} = 31.2 Hz), 128.9 (q, ³*J*_{C,F} = 3.2 Hz), 128.8, 127.5, 126.5, 123.6 (m, ³*J*_{C,F} ~ 3.1 Hz), 123.3 (q, ¹*J*_{C,F} = 274.2 Hz), 123.2 (q, ¹*J*_{C,F} = 272.3 Hz), 122.9, 122.8, 112.7, 110.3, 107.1, 67.5, 61.4, 43.7, 43.2, 40.4, 36.6, 32.9, 32.1, 26.8. LCMS (ESI) *m/z*: 536.2131 calcd for C₂₈H₂₈F₆N₃O⁺ [*M* + *H*]⁺; Found 536.2120.

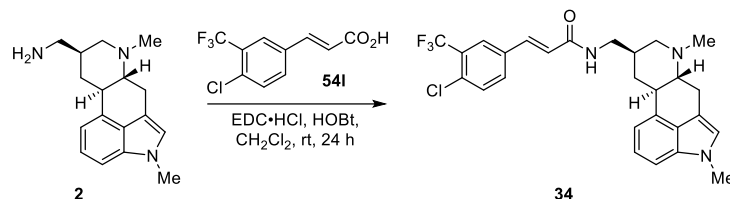
N-(2-Fluoro-4-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**33**)



As a modification of General Procedure A, amine **2** (47 mg, 0.17 mmol) was combined with EDC·HCl (34 mg, 0.18 mmol), HOBT (27 mg, 0.17 mmol), and 2-fluoro-4-trifluoromethylcinnamic acid **54k** (32 mg, 0.14 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **33** as an oily solid (12 mg, 0.026 mmol, 19%). *R*_f = 0.54 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.72 (d, *J* = 15.8 Hz, 1H), 7.62 (dd, *J* = 8.1, ³*J*_{HF} ~ 7 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.37 (d, ³*J*_{HF} = 10.5 Hz, 1H), 7.18 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 5.83 (brs, 1H), 3.76 (s, 3H), 3.49–3.40 (m, 2H), 3.39 (dd, *J* = 14.7, 4.3 Hz, 1H), 3.07 (brd, *J* = 11.3 Hz, 1H), 2.97 (td, *J* = 10.2, 3.7 Hz, 1H), 2.72 (brd, *J* = 12.7 Hz, 1H), 2.68 (ddd, *J* = 14.4, 11.1, 1.4 Hz, 1H), 2.47 (s, 3H), 2.27–2.13 (m, 2H), 2.03 (t, *J* = 11.4 Hz, 1H), 1.20 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 165.4, 160.9 (d, ¹*J*_{CF} = 255.5 Hz), 134.5,

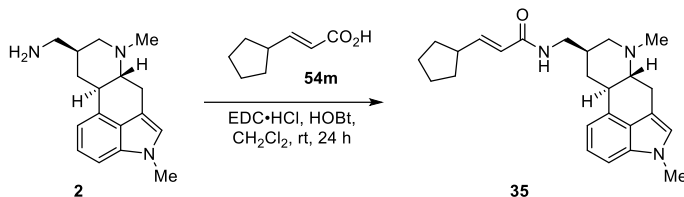
133.3, 133.0, 132.7 (dq, $^2J_{\text{CF}} = 33.8$ Hz, $^3J_{\text{CF}} = 8.5$ Hz), 130.5 (d, $^3J_{\text{CF}} = 3.3$ Hz), 126.6, 126.5 (d, $^2J_{\text{CF}} = 11.7$ Hz), 126.1 (d, $^3J_{\text{CF}} = 7.8$ Hz), 123.2 (dq, $^1J_{\text{CF}} = 272.1$ Hz, $^4J_{\text{CF}} = 2.3$ Hz), 122.8, 122.7, 121.4, 113.9 (dq, $^2J_{\text{CF}} = 25.4$ Hz, $^3J_{\text{CF}} = 3.9$ Hz), 112.6, 110.8, 107.0, 67.5, 61.6, 43.8, 43.5, 40.7, 36.9, 32.9, 32.3, 27.1. LCMS (ESI) m/z : 486.2163 calcd for $\text{C}_{27}\text{H}_{28}\text{F}_4\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 486.2165.

N-(2-Chloro-3-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**34**)



As a modification of General Procedure A, amine **2** (42 mg, 0.15 mmol) was combined with EDC·HCl (30 mg, 0.15 mmol), HOBT (24 mg, 0.15 mmol), and 4-chloro-3-trifluoromethylcinnamic acid **54I** (31 mg, 0.12 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **34** as an off-white amorphous solid (12 mg, 0.026 mmol, 19%). $R_f = 0.75$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, CDCl_3): δ 7.82 (s, 1H), 7.63 (d, $J = 15.6$ Hz, 1H), 7.57 (d, $J = 8.3$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.18 (dd, $J = 7.1, 8.1$ Hz, 1H), 7.11 (d, $J = 8.1$ Hz, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 6.73 (s, 1H), 6.48 (d, $J = 15.6$ Hz, 1H), 5.83 (brs, 1H), 3.75 (s, 3H), 3.48–3.40 (m, 2H), 3.38 (dd, $J = 14.7, 4.2$ Hz, 1H), 3.09 (brd, $J = 11.1$ Hz, 1H), 2.98 (brt, $J = 12.1$ Hz, 1H), 2.74–2.66 (m, 2H), 2.48 (s, 3H), 2.24–2.15 (m, 2H), 2.05 (t, $J = 11.3$ Hz, 1H), 1.22 (q, $J = 12.4$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3): δ 165.3, 138.7, 134.5, 134.0, 133.3 (q, $^3J_{\text{CF}} = 1.9$ Hz), 133.2, 132.2, 132.0, 129.1 (q, $^2J_{\text{CF}} = 31.5$), 126.6, 126.4 (q, $^3J_{\text{CF}} = 5.1$ Hz), 123.0, 122.8, 122.7, 122.7 (q, $^1J_{\text{CF}} = 273.5$ Hz), 112.7, 110.6, 107.0, 67.5, 61.5, 43.7, 43.4, 40.6, 36.8, 32.9, 32.2, 27.0. LCMS (ESI) m/z : 502.1868 calcd for $\text{C}_{27}\text{H}_{28}^{35}\text{ClF}_3\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 502.1868.

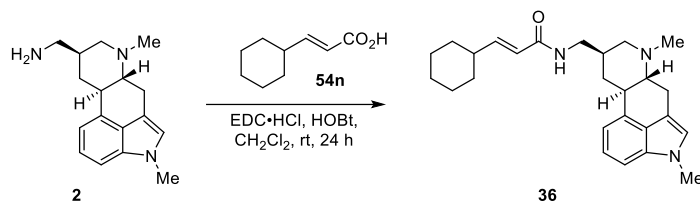
N-(3'-Cyclopentyl-*trans*-acryloyl) ergoline derivative (**35**)



As a modification of General Procedure A, amine **2** (48 mg, 0.18 mmol) was combined with EDC·HCl (36 mg, 0.18 mmol), HOBT (27 mg, 0.18 mmol), and 3-cyclopentylacrylic acid **54m** (34 mg, 0.14 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **35** as an oily solid (26 mg, 0.065 mmol, 47%). $R_f = 0.63$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, CDCl_3): δ 7.18 (dd, $J = 7.0, 8.2$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 6.89 (d, $J = 7.0$ Hz, 1H), 6.84

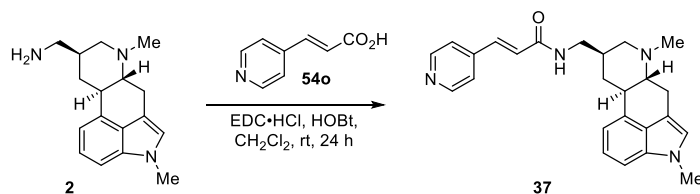
(dd, $J = 15.2, 8.0$ Hz, 1H), 6.72 (s, 1H), 5.77 (d, $J = 15.2$ Hz, 1H), 5.64 (brs, 1H), 3.74 (s, 3H), 3.44–3.29 (m, 3H), 3.04 (brd, $J = 11.4$ Hz, 1H), 2.96 (td, $J = 12.1, 3.7$ Hz, 1H), 2.70–2.64 (m, 2H), 2.57 (hextet, $J = 8.0$ Hz, 1H), 2.46 (s, 3H), 2.16–2.06 (m, 2H), 2.00 (t, $J = 11.4$ Hz, 1H), 1.86–1.79 (m, 2H), 1.73–1.66 (m, 2H), 1.64–1.56 (m, 2H), 1.44–1.37 (m, 2H), 1.18 (q, $J = 12.3$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3): δ 166.6, 149.3, 134.5, 133.3, 126.6, 122.8, 122.6, 121.7, 112.7, 110.7, 107.0, 67.5, 61.6, 43.4, 43.3, 42.8, 40.6, 36.9, 32.9, 32.7 (2C), 32.2, 27.0, 25.4 (2C). LCMS (ESI) m/z : 392.2696 calculated for $\text{C}_{25}\text{H}_{34}\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 392.2699.

N-(3'-Cyclohexyl-*trans*-acryloyl) ergoline derivative (**36**)



As a modification of General Procedure A, amine **2** (66 mg, 0.24 mmol) was combined with EDC·HCl (49 mg, 0.27 mmol), HOBT (42 mg, 0.27 mmol), and 3-cyclohexylacrylic acid **54n** (31 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **36** as an oily solid (43 mg, 0.11 mmol, 52%). $R_f = 0.60$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, CDCl_3): δ 7.18 (dd, $J = 7.1, 8.1$ Hz, 1H), 7.10 (d, $J = 8.1$ Hz, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 6.81 (dd, $J = 15.5, 6.8$ Hz, 1H), 6.72 (s, 1H), 5.74 (d, $J = 15.5$ Hz, 1H), 5.67 (brs, 1H), 3.74 (s, 3H), 3.41–3.28 (m, 3H), 3.04 (brd, $J = 11.2$ Hz, 1H), 2.96 (brt, $J = 10.8$ Hz, 1H), 2.71–2.63 (m, 2H), 2.46 (s, 3H), 2.17–2.08 (m, 3H), 1.99 (t, $J = 11.4$ Hz, 1H), 1.80–1.72 (m, 4H), 1.70–1.63 (brd, $J = 13.0$ Hz, 1H), 1.33–1.24 (m, 2H), 1.22–1.10 (m, 4H). ^{13}C NMR (175 MHz, CDCl_3): δ 166.7, 150.1, 134.5, 133.3, 126.6, 122.8, 122.6, 121.1, 112.7, 110.7, 106.9, 67.5, 61.6, 43.4, 43.3, 40.6, 40.4, 36.9, 32.9, 32.2, 32.1 (2C), 27.0, 26.1, 25.9 (2C). LCMS (ESI) m/z : 406.2853 calcd for $\text{C}_{26}\text{H}_{36}\text{N}_3\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 406.2869.

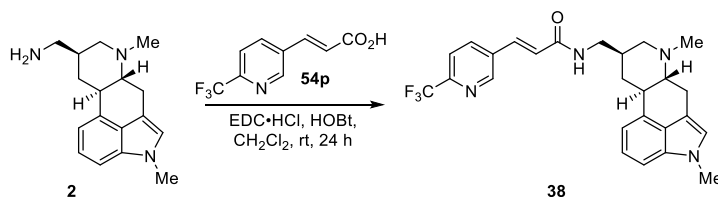
N-(3'-(4-Pyridyl)-*trans*-acryloyl) ergoline derivative (**37**)



As a modification of General Procedure A, amine **2** (42 mg, 0.16 mmol) was combined with EDC·HCl (37 mg, 0.20 mmol), HOBT (33 mg, 0.21 mmol), and 3-(4-pyridyl)acrylic acid **54o** (29 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **37** as a pale yellow amorphous solid (38 mg, 0.094 mmol, 61%). $R_f = 0.28$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, CDCl_3): δ 8.63 (d, $J = 4.8$ Hz, 2H), 7.58 (d, $J = 15.6$ Hz, 1H), 7.36 (d, $J = 4.8$ Hz, 2H), 7.18

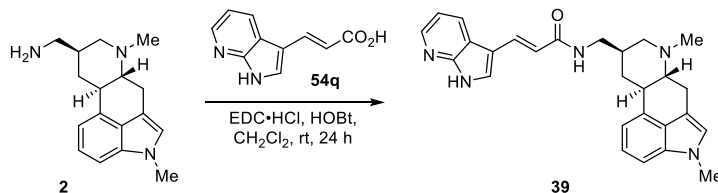
(dd, $J = 7.0, 8.2$ Hz, 1H), 7.12 (d, $J = 8.2$ Hz, 1H), 6.89 (d, $J = 7.0$ Hz, 1H), 6.74 (s, 1H), 6.61 (d, $J = 15.6$ Hz, 1H), 5.96 (brs, 1H), 3.76 (s, 3H), 3.49–3.40 (m, 2H), 3.39 (dd, $J = 14.8, 3.9$ Hz, 1H), 3.11 (brd, $J = 10.7$ Hz, 1H), 3.01 (brt, $J = 10.2$ Hz, 1H), 2.75–2.68 (m, 2H), 2.50 (s, 3H), 2.27–2.18 (m, 2H), 2.07 (t, $J = 11.4$ Hz, 1H), 1.23 (q, $J = 12.4$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3): δ 165.1, 150.7 (2C), 142.3, 138.7, 134.5, 133.0, 126.6, 125.2, 122.9, 122.8, 121.9 (2C), 112.7, 110.5, 107.1, 67.5, 61.5, 43.7, 43.6, 40.5, 36.7, 32.9, 32.2, 26.9. LCMS (ESI) m/z : 401.2336 calcd for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{O}^+$ [$\text{M} + \text{H}$] $^+$; Found 401.2318.

N-(3'-(4-Trifluoromethyl-3-pyridyl)-*trans*-acryloyl) ergoline derivative (**38**)



According to General Procedure A, *i*-Pr₂NEt (195 μL , 1.11 mmol) was added to a solution of amine **2** (100 mg, 0.37 mmol), EDC·HCl (85 mg, 0.44 mmol), HOBT (60 mg, 0.44 mmol), and 3-(4-trifluoromethyl-3-pyridyl)prop-2-enoic acid **54p** (97 mg, 0.44 mmol) in CH_2Cl_2 (10 mL). After stirring the reaction mixture overnight at rt for 24 h, it was diluted with CH_2Cl_2 (50 mL), washed with saturated Na_2CO_3 (2×40 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/ CH_2Cl_2) provided amide **38** as an off-white white solid (131 mg, 0.279 mmol, 75%). $R_f = 0.72$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, CDCl_3): δ 8.83 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 15.6$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.17 (dd, $J = 7.1, 8.2$ Hz, 1H), 7.10 (d, $J = 8.2$ Hz, 1H), 6.88 (d, $J = 7.1$ Hz, 1H), 6.72 (s, 1H), 6.62 (d, $J = 15.6$ Hz, 1H), 6.18 (brs, 1H), 3.74 (s, 3H), 3.47–3.39 (m, 2H), 3.37 (dd, $J = 14.6, 4.2$ Hz, 1H), 3.07 (brd, $J = 10.4$ Hz, 1H), 2.96 (brt, $J = 11.7$ Hz, 1H), 2.74–2.63 (m, 2H), 2.46 (s, 3H), 2.24–2.18 (m, 2H), 2.15 (td, $J = 10.7, 4.3$ Hz, 1H), 1.20 (q, $J = 12.4$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3): δ 164.9, 149.0, 148.4 (q, $^2J_{\text{CF}} = 35.0$ Hz), 136.1, 135.9, 134.5, 133.6, 133.1, 126.6, 125.2, 122.8, 122.7, 121.5 (q, $^1J_{\text{CF}} = 274.0$ Hz), 120.7 (q, $^3J_{\text{CF}} = 2.5$ Hz), 112.6, 110.6, 107.0, 67.4, 61.5, 43.8, 43.4, 40.6, 36.7, 32.9, 32.2, 27.0. LCMS (ESI) m/z : 469.2210 calcd for $\text{C}_{26}\text{H}_{28}\text{F}_3\text{N}_4\text{O}^+$ [$\text{M} + \text{H}$] $^+$; Found 469.2221.

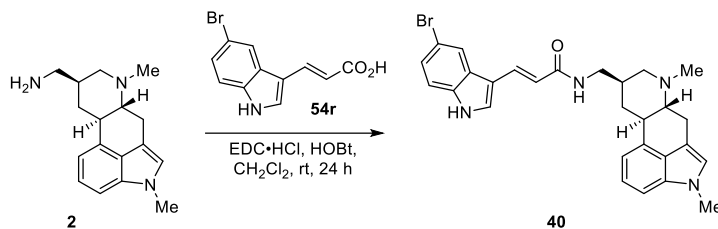
N-(3'-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*E*-acryloyl) ergoline derivative (**39**)



As a modification of General Procedure A, amine **2** (46 mg, 0.17 mmol) was combined with EDC·HCl (40 mg, 0.21 mmol), HOBT (34 mg, 0.22 mmol), and 3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylic acid **54q** (40 mg, 0.21 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **39** as an off-white amorphous solid (10 mg, 0.024 mmol, 14%). $R_f = 0.42$ (15%

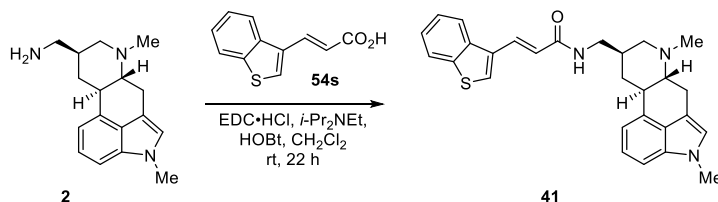
MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 10.75–10.61 (brs, 1H), 8.36 (d, *J* = 4.5 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 15.6 Hz, 1H), 7.58 (s, 1H), 7.21–7.15 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 5.92 (brs, 1H), 3.75 (s, 3H), 3.50–3.41 (m, 2H), 3.39 (dd, *J* = 14.7, 4.3 Hz, 1H), 3.14 (brd, *J* = 10.5 Hz, 1H), 3.00 (brdt, *J* = 10.7, 3.3 Hz, 1H), 2.75–2.67 (m, 2H), 2.49 (s, 3H), 2.26–2.17 (m, 2H), 2.07 (t, *J* = 11.4 Hz, 1H), 1.23 (q, *J* = 12.3 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 167.1, 149.6, 143.9, 134.5, 134.3, 133.2, 129.1, 128.5, 126.6, 122.9, 122.7, 118.4, 117.1, 117.0, 112.7, 112.2, 110.6, 107.0, 67.5, 61.6, 43.6, 43.4, 40.7, 36.9, 32.9, 32.3, 27.0. LCMS (ESI) *m/z*: 440.2445 calculated for C₂₇H₃₀N₅O⁺ [*M* + *H*]⁺; Found 440.2438.

N-(3'-(5-Bromoindol-3-yl)-*E*-acryloyl) ergoline derivative (**40**)



As a modification of General Procedure A, amine **2** (29 mg, 0.11 mmol) was combined with EDC·HCl (25 mg, 0.13 mmol), HOBT (22 mg, 0.14 mmol), and 3-(5-bromo-1*H*-indol-3-yl)acrylic acid **54r** (35 mg, 0.13 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **40** as an oily solid (10 mg, 0.024 mmol, 14%). ¹H NMR (700 MHz, CDCl₃): δ 9.62–9.55 (brs, 1H), 7.99 (s, 1H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.39 (s, 1H), 7.28 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.15 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 6.70 (s, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.09 (brs, 1H), 3.72 (s, 3H), 3.43–3.38 (m, 2H), 3.36 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.10 (brd, *J* = 9.9 Hz, 1H), 2.96 (brt, *J* = 10.4, 3.4 Hz, 1H), 2.72–2.65 (m, 2H), 2.45 (s, 3H), 2.26–2.18 (m, 1H), 2.15 (td, *J* = 10.7, 4.3 Hz, 1H), 2.03 (t, *J* = 11.4 Hz, 1H), 1.18 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 167.6, 136.0, 134.5, 134.4, 133.1, 129.8, 127.1, 126.5, 125.9, 123.0, 122.9, 122.7, 116.4, 114.5, 113.5, 113.0, 112.8, 110.5, 107.0, 67.5, 61.5, 43.7, 43.3, 40.5, 36.8, 32.9, 32.2, 26.9. LCMS (ESI) *m/z*: 517.1598 calcd for C₂₈H₃₀⁷⁹BrN₄O⁺ [*M* + *H*]⁺; Found 517.1595.

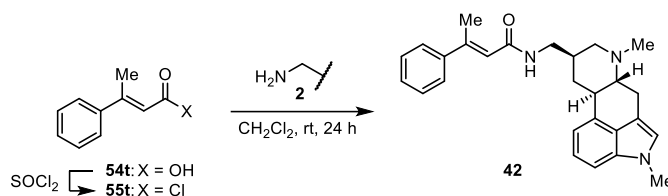
N-(3'-(3-Benzothiophenyl)-*E*-acryloyl) ergoline derivative (**41**)



According to General Procedure A, *i*-Pr₂NEt (61 μL, 0.37 mmol) was added to a solution of amine **2** (33 mg, 0.12 mmol), EDC·HCl (28 mg, 0.15 mmol), HOBT (20 mg, 0.15 mmol), and 3-(3-benzothiophenyl)prop-2-enoic acid **54s** (25 mg, 0.12 mmol) in CH₂Cl₂ (5 mL). After stirring the reaction mixture overnight at rt for 24 h, it was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 ×

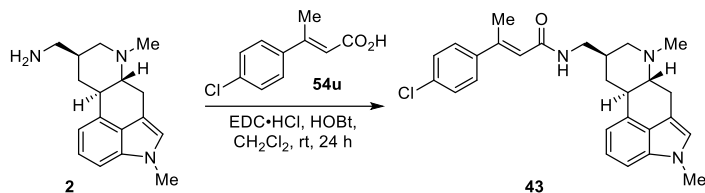
20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/CH₂Cl₂) provided amide **41** as a yellow oil (51 mg, 0.11 mmol, 91%). ¹H NMR (700 MHz, CDCl₃): 8.04 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 15.6 Hz, 1H), 7.86 (d *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.44 (appt, *J* = 7.5 Hz, 1H), 7.38 (appt, *J* = 7.5 Hz, 1H), 7.17 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.71 (s, 1H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.16 (brs, 1H), 3.74 (s, 3H), 3.50–3.45 (m, 1H), 3.45–3.40 (m, 1H), 3.38 (dd, *J* = 14.5, 4.2 Hz, 1H), 3.21 (brd, *J* = 10.8 Hz, 1H), 3.10 (brdt, *J* = 9.4 Hz, 1H), 2.81 (brt, *J* = 12.9 Hz, 1H), 2.71 (brd, *J* = 12.8 Hz, 1H), 2.55 (s, 3H), 2.35–2.27 (m, 2H), 2.17 (t, *J* = 11.5 Hz, 1H), 1.23 (q, *J* = 12.3 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 166.4, 140.6, 137.5, 134.5, 133.2, 132.6, 132.1, 126.9, 126.4, 125.0, 124.9, 123.1, 122.9, 122.8, 122.3, 121.4, 112.8, 110.0, 107.2, 67.6, 61.3, 43.4, 43.0, 40.2, 36.5, 32.9, 32.0, 26.6. LCMS (ESI) *m/z*: 456.2104 calcd for C₂₈H₃₀N₃OS⁺ [M + H]⁺; Found 456.2104.

N-((*E*)-3-Phenylbut-2-enoyl) ergoline derivative (**42**)



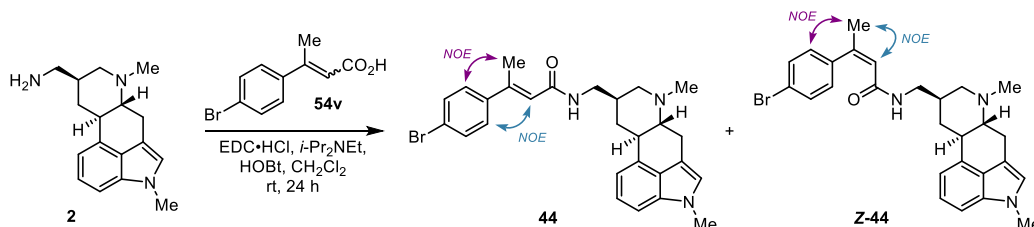
SOCl₂ (2 mL) was added to a solution of 3-phenyl-2-buten-1-ol **54t** (40.5 mg, 0.25 mmol) in CH₂Cl₂ (3 mL) and heated to reflux for 6 h. The solution was then cooled to rt and concentrated in vacuo. The crude acid chloride **55t** (44.9 mg) was combined with amine **2** (75.0 mg, 0.28 mmol) and stirred in CH₂Cl₂ at rt for 24 h. The reaction mixture was diluted in CH₂Cl₂, washed with sat. Na₂CO₃ (50 mL), and brine (50 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (80:20 CH₂Cl₂/MeOH) to provide the β-methyl cinnamide **42** (36.1 mg, 0.087 mmol, 53%) as an oily solid. *R*_f = 0.52 (15% MeOH/CH₂Cl₂). For NMR characterization, a small amount of formic acid (approximately 4 equiv by integration of protons by ¹H NMR) was added to the CDCl₃ to improve solubility. ¹H NMR (700 MHz, CDCl₃): δ 10.5–9.2 (brs, 4H)*, 8.14 (s, 4H)*, 7.46 (d, *J* = 6.7 Hz, 2H), 7.39–7.31 (m, 3H), 7.20 (dd, *J* = 7.0, 8.1 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.09–7.03 (brs, 1H), 6.88 (d, *J* = 7.0 Hz, 1H), 6.78 (s, 1H), 6.20 (s, 1H), 3.76 (s, 3H), 3.75–3.69 (m, 1H), 3.63–3.53 (m, 2H), 3.45 (dd, *J* = 14.2, 4.5 Hz, 1H), 3.34–3.26 (m, 2H), 3.04–2.97 (m, 1H), 2.95 (s, 3H), 2.83–2.71 (m, 3H), 2.55 (s, 3H), 1.38 (q, *J* = 12.3 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 168.4, 165.1*, 152.0, 142.6, 134.5, 129.4, 128.8, 128.6 (2C), 126.3 (2C), 125.8, 132.5, 123.2, 119.3, 113.3, 108.1, 106.8, 68.4, 60.2, 42.0, 41.9, 38.7, 34.6, 33.1, 30.7, 24.7, 17.9. LCMS (ESI) *m/z*: 414.2540 calcd for C₂₇H₃₂N₃O⁺ [M + H]⁺; Found 414.2526. * Asterisks indicate signals for formic acid.

N-((*E*)-3-(4-Chlorophenyl)but-2-enoyl) ergoline derivative (**43**)



As a modification of General Procedure A, amine **2** (93 mg, 0.35 mmol) was combined with EDC·HCl (68 mg, 0.35 mmol), HOBT (54 mg, 0.35 mmol), and 3-(4-chlorophenyl)but-2-enoic acid **54u** (56 mg, 0.29 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **43** as an oily solid (95 mg, 0.21 mmol, 74%). *R*_f = 0.50 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.18 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.72 (s, 1H), 6.04 (s, 1H), 5.89 (brs, 1H), 3.75 (s, 3H), 3.40–3.32 (m, 3H), 3.07 (brd, *J* = 11.4 Hz, 1H), 2.97 (brt, *J* = 10.6, 3.8 Hz, 1H), 2.72–2.65 (m, 2H), 2.54 (s, 3H), 2.47 (s, 3H), 2.24–2.13 (m, 2H), 2.02 (t, *J* = 11.4 Hz, 1H), 1.19 (q, *J* = 12.3 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 166.9, 149.6, 141.1, 134.5, 134.4, 133.2, 128.7 (2C), 127.6 (2C), 126.6, 122.8, 122.7, 120.3, 112.6, 110.6, 107.0, 67.5, 61.6, 43.4, 43.3, 40.6, 36.7, 32.9, 32.3, 27.0, 17.7. LCMS (ESI) *m/z*: 448.2150 calcd for C₂₇H₃₁³⁵ClN₃O⁺ [*M* + *H*]⁺; Found 448.2154.

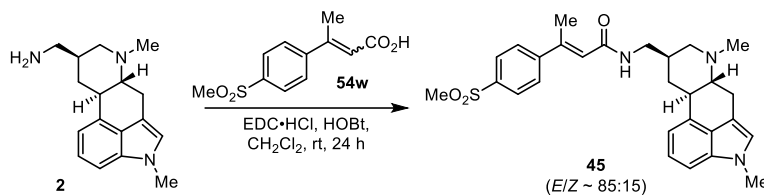
N-((*E*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**44**)



According to General Procedure A, *i*-Pr₂NEt (195 μL, 1.11 mmol) was added to a solution of amine **2** (100 mg, 0.37 mmol), EDC·HCl (85 mg, 0.44 mmol), HOBT (60 mg, 0.44 mmol), and 3-(4-bromophenyl)prop-2-enoic acid **54v** (107 mg, 0.44 mmol, *E/Z* ~78:22) in CH₂Cl₂ (10 mL). After stirring the reaction mixture overnight at rt for 24 h, it was diluted with CH₂Cl₂ (50 mL), washed with saturated Na₂CO₃ (2 × 40 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/CH₂Cl₂) provided amide **44** as an off-white white solid (33 mg, 0.033 mmol, 18%) and the isomer **Z-44** as an oily solid (24 mg) that was estimated to be 75–80% pure by ¹H NMR. *E/Z* stereochemistry was determined by NOESY NMR experiments (pages S103 and S106). The impure sample of **Z-44** was used for NMR experiments, but was not used in biological assays or purified further. **44** (*E*-isomer): *R*_f = 0.30 (5% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.18 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 1H), 6.04 (s, 1H), 5.73 (brs, 1H), 3.75 (s, 3H), 3.41–3.34 (m, 3H), 3.10 (brd, *J* = 10.7 Hz, 1H), 3.01 (brt, *J* = 9.2 Hz, 1H), 2.75–2.67 (m, 2H), 2.54 (s, 3H), 2.50 (s, 3H), 2.24–2.15 (m, 2H), 2.06 (t, *J* = 11.2 Hz, 1H), 1.21 (q, *J* = 12.4 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 166.9, 149.8, 141.6, 134.5,

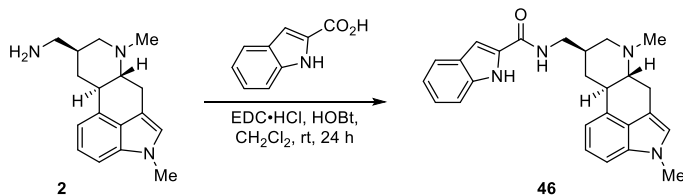
133.2, 131.7 (2C), 127.9 (2C), 126.6, 122.9, 122.8, 122.7, 120.4, 112.7, 110.6, 107.0, 67.5, 61.6, 43.4, 43.3, 40.5, 36.8, 32.9, 32.3, 27.0, 17.7. LCMS (ESI) m/z : 492.1645 calcd for $C_{27}H_{31}^{79}BrN_3O^+$ [$M + H$] $^+$; Found 492.1653.

N-((*E*)-3-(4-Methylsulfonylphenyl)but-2-enoyl) ergoline derivative (**45**)



As a modification of General Procedure A, amine **2** (81 mg, 0.30 mmol) was combined with EDC·HCl (61 mg, 0.32 mmol), HOBT (48 mg, 0.31 mmol), and 3-(4-methanesulfonylphenyl)but-2-enoic acid **54w** (60 mg, 0.30 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **45** as a mixture of *E/Z* isomers ~85:15 (108 mg, 0.22 mmol, 88%). R_f (*E/Z*) = 0.52/0.48 (15% MeOH/ CH_2Cl_2). 1H NMR (700 MHz, $CDCl_3$) (*E/Z*): δ 7.93/7.89 (d, J = 8.5 Hz, 2H), 7.61/7.68 (d, J = 8.5 Hz, 2H), 7.18 (dd, J = 8.1, 7.1 Hz, 1H), 7.12/7.11 (d, J = 8.1 Hz, 1H), 6.90/6.76 (d, J = 7.1 Hz, 1H), 6.74/6.72 (s, 1H), 6.11/5.80 (q, J = 1.2 Hz, 1H), 5.89/5.49 (brs, 1H), 3.76/3.75 (s, 3H), 3.41–3.36 (m, 3H), 3.15–3.10 (m, 1H), 3.07/2.89 (s, 3H), 3.03 (td, J = 9.9, 4.2 Hz, 1H), 2.76–2.69 (m, 2H), 2.58 (q, J = 1.2 Hz, 3H), 2.51/2.40 (s, 3H), 2.26–2.19 (m, 2H), 2.08 (t, J = 11.4 Hz, 1H), 1.22/1.04 (q, J = 12.4 Hz, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) (*E/Z*): δ 166.4, 148.9/144.5, 148.4/140.9, 140.3/140.1, 134.5, 133.0/132.9, 127.8/128.0 (2C), 127.3/126.8 (2C), 126.6/126.5, 122.9, 122.8, 122.6/122.8, 112.7/112.5, 110.4/110.3, 107.1/107.2, 67.5/67.4, 61.5/61.2, 51.0, 44.7/44.4, 43.3 (2C), 40.5, 36.7/36.6, 32.9, 32.2/31.9, 36.9/27.0, 17.9/17.7. LCMS (ESI) m/z : 492.2315 calcd for $C_{28}H_{34}N_3O_3S^+$ [$M + H$] $^+$; Found 492.2320.

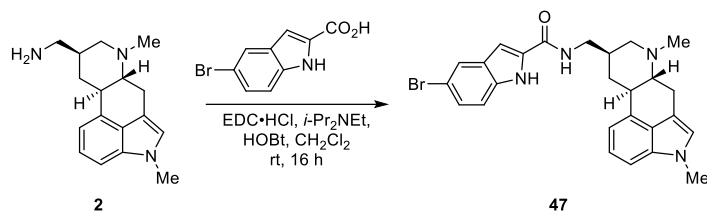
N-2'-Indoloyl ergoline derivative (**46**)



As a modification of General Procedure A, amine **2** (40 mg, 0.15 mmol) was combined with EDC·HCl (36 mg, 0.19 mmol), HOBT (31 mg, 0.21 mmol), and indole-2-carboxylic acid (30 mg, 0.19 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide cinnamide **46** as an off-white amorphous solid (32 mg, 0.078 mmol, 53%). R_f = 0.52 (15% MeOH/ CH_2Cl_2). 1H NMR (700 MHz, $CDCl_3$): δ 9.60–9.53 (brs, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.27 (dd, J = 8.0, 7.5 Hz, 1H), 7.18 (dd, J = 8.2, 7.1 Hz, 1H), 7.13 (dd, J = 8.5, 7.5 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H),

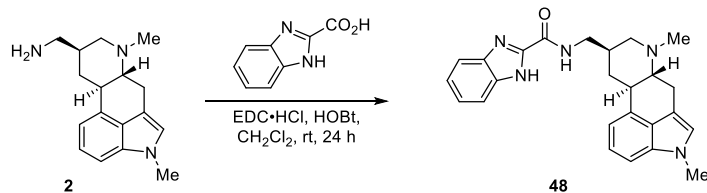
6.92 (s, 1H), 6.88 (d, $J = 7.1$ Hz, 1H), 6.73 (s, 1H), 6.54 (brs, 1H), 3.75 (s, 3H), 3.53 (dd, $J = 13.7, 6.9$ Hz, 1H), 3.50 (dd, $J = 13.7, 5.5$ Hz, 1H), 3.38 (dd, $J = 14.5, 4.2$ Hz, 1H), 3.18 (brd, $J = 11.2$ Hz, 1H), 3.05 (brt, $J = 12.1$ Hz, 1H), 2.78–2.69 (m, 2H), 2.50 (s, 3H), 2.35–2.27 (m, 1H), 2.23 (td, $J = 10.5, 4.1$ Hz, 1H), 2.11 (t, $J = 11.4$ Hz, 1H), 1.24 (q, $J = 12.2$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3): δ 162.0, 136.5, 134.5, 132.9, 130.8, 127.8, 126.5, 124.7, 122.9, 122.8, 122.1, 120.8, 112.7, 112.1, 110.3, 107.1, 102.4, 67.5, 61.4, 43.5, 43.2, 40.4, 36.7, 39.9, 32.1, 26.9. LCMS (ESI) m/z : 413.2336 calculated for $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 413.2343.

N-(5'-Bromoindol-2'-oyl) ergoline derivative (47)



According to General Procedure A, *i*-Pr₂NEt (55 μL , 0.33 mmol) was added to a solution of amine **2** (28 mg, 0.10 mmol), EDC·HCl (24 mg, 0.12 mmol), HOBT (17 mg, 0.12 mmol), and 5-bromoindole-2-carboxylic acid (30 mg, 0.12 mmol) in CH_2Cl_2 (5 mL). After stirring the reaction mixture overnight at rt for 16 h, it was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×15 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. Flash chromatography (0→15% MeOH/ CH_2Cl_2) provided amide **45** as an off-white solid (26 mg, 0.052 mmol, 50%). $R_f = 0.62$ (15% MeOH/ CH_2Cl_2). ^1H NMR (700 MHz, $\text{DMSO}-d_6$): δ 11.83–11.80 (brs, 1H), 8.67 (brt, $J = 5.8$ Hz, 1H), 7.86 (d, $J = 1.7$ Hz, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 7.29 (dd, $J = 8.7, 1.8$ Hz, 1H), 7.17 (d, $J = 1.4$ Hz, 1H), 7.16 (d, $J = 8.2$ Hz, 1H), 7.06 (dd, $J = 7.1, 8.2$ Hz, 1H), 6.94 (s, 1H), 6.80 (d, $J = 7.1$ Hz, 1H), 3.72 (s, 3H), 3.31–3.23 (m, 3H), 3.13–3.03 (m, 1H), 2.92–2.81 (m, 1H), 2.68 (d, $J = 12.3$ Hz, 1H), 2.61–2.53 (m, 1H), 2.43 (brs, 3H), 2.24–1.96 (m, 3H), 1.09 (q, $J = 11.9$ Hz, 1H). ^{13}C NMR (175 MHz, $\text{DMSO}-d_6$): δ 160.8, 135.0, 134.0, 133.1, 132.9, 128.9, 126.1, 125.8, 123.6, 123.0, 122.1, 114.3, 112.1, 112.0, 109.7, 107.0, 101.9, 67.1, 61.2, 43.0, 42.8, 39.8, 35.9, 32.4, 32.1, 26.4. LCMS (ESI) m/z : 491.1441 calcd for $\text{C}_{26}\text{H}_{28}^{79}\text{BrN}_4\text{O}^+$ $[\text{M} + \text{H}]^+$; Found 491.1430.

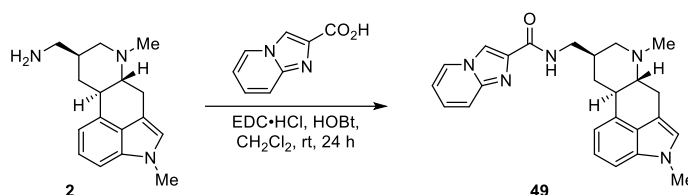
N-(2'-Benzimidazoloyl) ergoline derivative (48)



As a modification of General Procedure A, amine **2** (41 mg, 0.15 mmol) was combined with EDC·HCl (38 mg, 0.19 mmol), HOBT (31 mg, 0.20 mmol), and benzimidazole-2-carboxylic acid (31 mg, 0.19 mmol) in CH_2Cl_2 (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 (2×20 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/ CH_2Cl_2) to provide

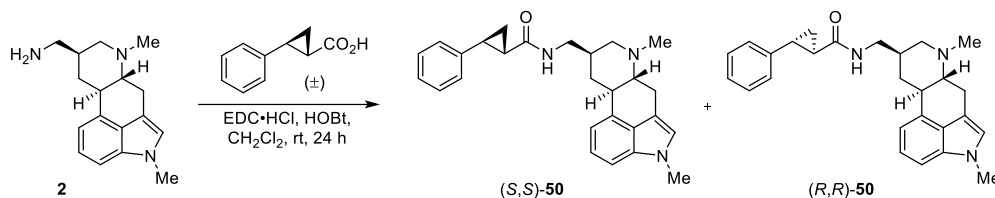
cinnamide **48** as an off-white amorphous solid (29 mg, 0.070 mmol, 45%). R_f = 0.59 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 12.25–12.00 (brs, 1H), 8.12–8.06 (brs, 1H), 7.81 (d, J = 7.1 Hz, 1H), 7.57 (d, J = 7.1 Hz, 1H), 7.38–7.31 (brs, 2H), 7.14 (dd, J = 7.1, 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.86 (d, J = 7.1 Hz, 1H), 6.72 (s, 1H), 3.74 (s, 3H), 3.61 (dd, J = 13.1, 6.1 Hz, 1H), 3.55 (dd, J = 13.1, 6.8 Hz, 1H), 3.36 (dd, J = 14.1, 3.6 Hz, 1H), 3.15 (brd, J = 10.7 Hz, 1H), 2.98 (brt, J = 10.5 Hz, 1H), 2.80 (d, J = 12.5 Hz, 1H), 2.67 (dd, J = 14.1, 11.5 Hz, 1H), 2.43 (s, 3H), 2.40–2.32 (m, 1H), 2.16 (brt, J = 9.8 Hz, 1H), 2.06 (t, J = 11.2 Hz, 1H), 1.27 (q, J = 12.5 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 159.9, 145.1, 143.0, 134.5, 134.4, 133.3, 126.6, 125.1, 123.6, 122.9, 122.6, 120.6, 112.7, 112.6, 110.8, 106.9, 67.5, 61.6, 43.8, 43.4, 40.6, 36.6, 32.9, 32.4, 27.0. LCMS (ESI) m/z : 414.2288 calcd for C₂₅H₂₈N₅O⁺ [M + H]⁺; Found 414.2270.

N-(Imidazo[1,2-*a*]pyridine-2'-oyl) ergoline derivative (**49**)



As a modification of General Procedure A, amine **2** (41 mg, 0.15 mmol) was combined with EDC·HCl (36 mg, 0.19 mmol), HOBT (32 mg, 0.21 mmol), and imidazo[1,2-*a*]pyridine-2-carboxylic acid (30 mg, 0.18 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **49** as an off-white amorphous solid (30 mg, 0.072 mmol, 48%). R_f = 0.50 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 8.17–8.12 (brs, 2H), 7.58 (d, J = 9.2 Hz, 1H), 7.55–7.50 (brs, 1H), 7.27–7.23 (m, 1H), 7.18 (dd, J = 7.1, 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 6.85 (t, J = 6.7 Hz, 1H), 6.72 (s, 1H), 3.75 (s, 3H), 3.55 (dd, J = 13.2, 6.1 Hz, 1H), 3.47 (dd, J = 13.2, 6.8 Hz, 1H), 3.38 (dd, J = 14.6, 4.0 Hz, 1H), 3.15 (brd, J = 10.1 Hz, 1H), 3.00 (m, 1H), 2.78 (brd, J = 12.7 Hz, 1H), 2.74–2.65 (m, 1H), 2.48 (s, 3H), 2.34–2.25 (m, 1H), 2.23–2.14 (m, 1H), 2.13–2.05 (m, 1H), 1.29 (q, J = 12.3 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 163.0, 144.7, 140.2, 134.5, 133.5, 126.6, 126.5, 126.1, 122.9, 122.6, 118.3, 114.3, 113.5, 112.8, 110.8, 106.9, 67.5, 61.6, 43.4, 43.1, 40.6, 36.8, 32.9, 32.3, 27.0. LCMS (ESI) m/z : 414.2288 calcd for C₂₅H₂₈N₅O⁺ [M + H]⁺; Found 414.2233.

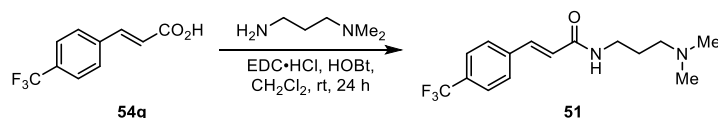
*N*¹,*N*⁶-Dimethylergoline 2'-Phenylcyclopropane-1'-carboxamide (**50**)



As a modification of General Procedure A, amine **2** (54 mg, 0.20 mmol) was combined with EDC·HCl (43 mg, 0.22 mmol), HOBT (33 mg, 0.22 mmol), and (±)-*trans*-2-phenylcyclopropane-1-carboxylic acid (27 mg, 0.17 mmol) in CH₂Cl₂ (15 mL) and stirred at rt for 24 h. The reaction mixture was diluted with

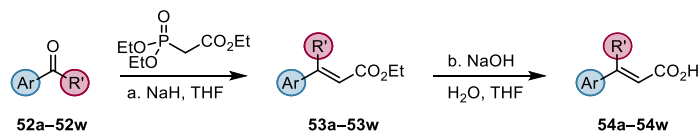
CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (0→20% MeOH/CH₂Cl₂) to provide cinnamides **50** as a 1:1 mixture of *trans*-cyclopropane diastereomers (35 mg, 0.084 mmol, 50%). *R*_f = 0.48 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.28/7.27 (t, *J* = 7.7 Hz, 2H), 7.21–7.17 (m, 2H), 7.13–7.09 (m, 3H), 6.89 (d, *J* = 7.1 Hz, 1H), 6.73 (s, 1H), 5.98/5.97 (brs, 1H), 3.75 (s, 3H), 3.38 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.35–3.25 (m, 2H), 3.13–3.08 (m, 1H), 3.05–2.99 (m, 1H), 2.78–2.71 (m, 1H), 2.70–2.65 (m, 1H), 2.54–2.49 (m, 1H), 2.51/2.50 (s, 3H), 2.25–2.14 (m, 2H), 2.05/2.04 (t, *J* = 11.4 Hz, 1H), 1.69–1.62 (m, 2H), 1.28–1.23 (m, 1H), 1.17 (q, *J* = 12.2 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 172.3/172.2, 141.0/140.9, 134.5, 132.9/132.8, 128.6 (2C), 126.5, 126.4, 126.1 (2C), 122.9, 122.7, 112.7, 110.3/110.2, 107.1/107.0, 67.5, 61.4/61.3, 43.7/43.6, 43.2/43.1, 40.3/40.2, 36.5, 32.9, 32.1/32.0, 26.9/26.8, 26.8/26.7, 25.2/25.1, 16.2/16.1. LCMS (ESI) *m/z*: 414.2540 calcd for C₂₇H₃₂N₃O⁺ [*M* + *H*]⁺; Found 414.2548.

(*E*)-*N*-(3-(Dimethylamino)propyl)-3-(4-trifluoromethylphenyl)acrylamide (**51**)



As a modification of General Procedure A, *N,N*-dimethylaminopropylamine (63 mg, 0.61 mmol) was combined with EDC·HCl (147 mg, 0.765 mmol), HOBT (119 mg, 0.777 mmol), and 4-trifluoromethylcinnamic acid **54g** (167 mg, 0.774 mmol) in CH₂Cl₂ (30 mL) and stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (25 mL), washed with saturated Na₂CO₃ (2 × 20 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (5→20% MeOH/CH₂Cl₂) to provide cinnamide **51** as an oily solid (81 mg, 0.27 mmol, 44%). *R*_f = 0.48 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, CDCl₃): δ 7.63–7.57 (m, 5H), 7.51–7.46 (brs, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 3.49 (dq, *J* = 6.2, 5.8 Hz, 2H), 2.45 (t, *J* = 6.2 Hz, 2H), 2.28 (s, 6H), 1.73 (p, *J* = 6.2 Hz, 2H). ¹³C NMR (175 MHz, CDCl₃): δ 165.3, 138.7, 138.6, 131.2 (q, ²*J*_{CF} = 32.6 Hz), 128.0 (2C), 125.9 (q, ³*J*_{CF} = 3.8 Hz, 2C), 124.1 (q, ¹*J*_{CF} = 272.1 Hz), 124.0, 59.0, 45.6 (2C), 40.1, 25.9. LCMS (ESI) *m/z*: 301.1522 calcd for C₁₅H₂₀F₃N₂O⁺ [*M* + *H*]⁺; Found 301.1525.

General Procedure C

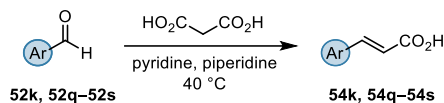


Substituted cinnamic- and acrylic acids were synthesized in a two-step sequence, as previously reported by Liu et al.¹⁵ and Li et al.¹⁶ Triethyl phosphonoacetate (1.5 equiv) was added slowly to a

15. Liu, R.; Yan, Z.; Ni, Y.; Song, K.; Shen, K.; Lin, S.; Pan, Q. Pd(II)/bipyridine-catalyzed conjugate addition of arylboronic acids to α,β -unsaturated carboxylic acids. Synthesis of β -quaternary carbons substituted carboxylic acids. *J. Org. Chem.* **2017**, 82, 8023–8030 (doi:10.1021/acs.joc.7b01248).
16. Li, Y.; Dong, K.; Wang, Z.; Ding, K. Rhodium(I)-catalyzed enantioselective hydrogenation of substituted acrylic acids with sterically similar β,β -diaryls. *Angew. Chem. Int. Ed.* **2013**, 52, 6748–6752 (doi: 10.1002/anie.201302349).

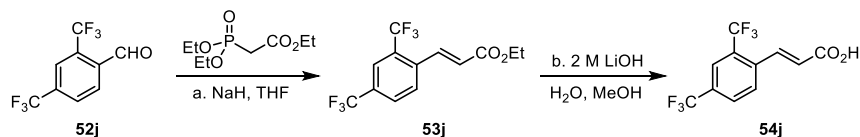
suspension of NaH (1.5 equiv, 60% w/w dispersion in mineral oil) in THF at 0 °C. The mixture was allowed to warm to rt and stirred until gas evolution had ceased (typically for ~30 min). A solution of the aldehyde or ketone (**52a–52w**, 1.0 equiv) in THF was then added slowly dropwise at 0 °C and the reaction stirred at rt for 16–24 h. The reaction mixture was quenched with NH₄Cl, extracted with EtOAc, washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude esters **53** were purified by chromatography (MeOH/CH₂Cl₂) on silica gel. *E/Z* ratios of disubstituted acrylates **53** and **54** were determined by integration of peaks in ¹H NMR spectra. *E/Z* ratios for β-methyl (R' = Me) acrylates **53** and/or acrylic acids **54** were determined by NOESY NMR experiments (Brüker pulse program: noesygpphpp). NOESY spectra for **44**, **Z-44**, and **54v** are provided.

General Procedure D



Some of the arylacrylic acids in this study were prepared from the condensation of the appropriate benzaldehyde with malonic acid, according to methods described previously.^{17,18} A solution of aldehyde **52** (1 equiv) and malonic acid (3 equiv) in pyridine/piperidine (~100:1) was stirred for ~40 h at 40 °C. The solution was concentrated under reduced pressure and the resulting oil was taken up in 2 M NaOH and washed with EtOAc. The aqueous NaOH solution was transferred to an Erlenmeyer flask and acidified while stirring at 0 °C to pH ~2 with 12 M HCl. The acrylic acid product **54** could be collected by filtration and/or by extraction of the aqueous solution with EtOAc.

(*E*)-2,4-Di(trifluoromethyl)cinnamic acid (**54j**)



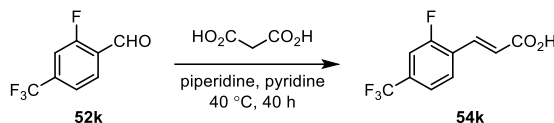
Triethyl phosphonoacetate (252 mg, 1.12 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (44 mg, 1.10 mmol, 60% w/w dispersion in mineral oil) in THF (5 mL). After gas evolution had ceased (~15 min), a solution of 2,4-bis(trifluoromethyl)benzaldehyde (172 mg, 0.711 mmol) in THF (5 mL) was added slowly at 0 °C and stirred at rt for 24 h. The reaction mixture was then diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure to provide ester **53j** as a viscous oily residue (177 mg) that was used in the subsequent reaction without additional purification. *R*_f = 0.52 (15% EtOAc/Hex). LCMS (ESI) *m/z*: 313.0658 calcd for C₁₃H₁₁F₆O₂⁺ [M + H]⁺; Found 313.0639.

A 2.0 M aqueous solution of LiOH (1.0 mL, 2.0 mmol) was added to a solution of the ester **53j** (177 mg, ~0.566 mmol) in MeOH (5 mL) and stirred at rt for 24 h. The reaction mixture was acidified with

- Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G.; Armstrong, M. D. Preparation and properties of β-3-indolyl compounds related to tryptophan metabolism. *J. Org. Chem.* **1958**, *23*, 1171–1178 (doi:10.1021/jo01102a025).
- Kinsman, A. C.; Kerr, M. A. The total synthesis of (+)-hapalindole Q by an organomediated Diels–Alder reaction. *J. Am. Chem. Soc.* **2003**, *125*, 14120–14125 (doi:10.1021/ja036191y).

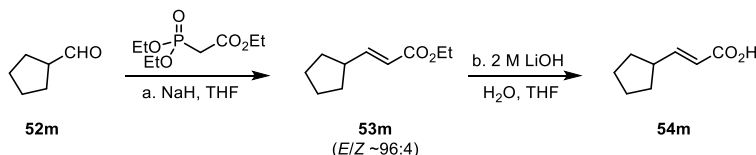
10% HCl (15 mL) and the precipitate was collected by filtration. The wet precipitate was dissolved in CH₂Cl₂, dried over Na₂SO₄, and concentrated under reduced pressure to provide the cinnamic acid **54j** as a white amorphous solid (142 mg, 0.498 mmol, 70% over 2 steps). ¹H NMR (700 MHz, CDCl₃): δ 12.5–10.5 (brs, 1H), 8.17 (dq, *J* = 15.8, 2.1 Hz, 1H), 7.98 (s, 1H), 7.87 (s, 2H), 6.51 (d, *J* = 15.8 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 170.9, 141.1 (q, ⁴*J*_{CF} = 2.0 Hz), 136.7, 132.2 (q, ²*J*_{CF} = 33.8 Hz), 129.9 (q, ²*J*_{CF} = 31.7 Hz), 129.2 (q, ³*J*_{CF} = 3.3 Hz), 129.0, 124.0, 123.7 (m), 123.3 (q, ¹*J*_{CF} = 274.3 Hz), 123.2 (q, ¹*J*_{CF} = 272.6 Hz). LCMS (ESI) *m/z*: 285.0345 calcd for C₁₁H₇F₆O₂⁺ [M + H]⁺; Found 285.0334.

(*E*)-2-Fluoro-4-(trifluoromethyl)cinnamic acid (**54k**)



2-Fluoro-4-(trifluoromethyl)benzaldehyde **52k** (322 mg, 1.67 mmol) and malonic acid (526 mg, 5.06 mmol) were stirred with piperidine (50 μL) in pyridine (5 mL) at 40 °C for 40 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in 1 M NaOH (15 mL) and washed with EtOAc (25 mL), and acidified with stirring at 0 °C to pH ~2 with 12 M HCl. The resulting precipitate was collected by filtration to provide acid **54k** as a pale yellow amorphous solid (190 mg, 0.810 mmol, 48%). *R*_f = 0.05–0.30 (15% MeOH/CH₂Cl₂). ¹H NMR (700 MHz, acetone-*d*₆): δ 12.0–10.0 (brs, 1H), 8.04 (app t, *J* = 7.6, 1H), 7.80 (d, *J* = 16.2 Hz, 1H), 7.64–7.56 (m, 2H), 6.74 (d, *J* = 16.2 Hz, 1H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 167.1, 161.5 (q, ¹*J*_{CF} = 253.6 Hz), 135.8 (d, *J*_{CF} = 2.6 Hz), 133.5 (dq, ²*J*_{CF} = 33.5 Hz, ³*J*_{CF} = 8.5 Hz), 131.2 (d, *J*_{CF} = 3.3 Hz), 127.2 (d, ²*J*_{CF} = 11.7 Hz), 124.6 (d, ³*J*_{CF} = 5.2 Hz), 124.2 (dq, ¹*J*_{CF} = 271.6 Hz, ⁴*J*_{CF} = 2.6 Hz), 122.5 (p, ³*J*_{CF} = ⁴*J*_{CF} = 3.6 Hz), 114.4, (dq, ²*J*_{CF} = 25.4 Hz, ³*J*_{CF} = 3.9 Hz). LCMS (ESI) *m/z*: 233.0231 calcd for C₁₀H₅F₄O₂[−] [M − H][−]; Found 233.0231.

(*E*)-3-Cyclopentylacrylic acid (**54m**)

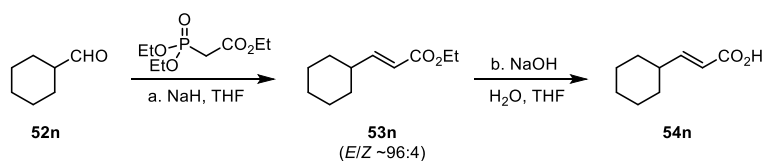


Triethyl phosphonoacetate (3.645 g, 16.26 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (650 mg, 16.25 mmol, 60% w/w dispersion in mineral oil) in THF (25 mL). After gas evolution had ceased (~20 min), a solution of cyclopentane carboxaldehyde (1.064 g, 10.84 mmol) in THF (5 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (0→20% EtOAc/Hex) to provide ester **53m** (*E/Z* ~96:4) as a colorless oil (1.407 g, 8.368 mmol, 77%). ¹H NMR (700 MHz, CDCl₃): δ 6.89 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.74 (d, *J* = 15.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.54 (h, *J* = 8.1 Hz, 1H), 1.82–1.75 (m, 2H), 1.69–1.61 (m, 2H), 1.59–1.52 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 167.0, 153.5,

119.4, 60.1, 42.9, 32.4 (2C), 25.3 (2C), 14.3. The synthesis of ester **53m** has been reported previously.^{19,20}

A 2.0 M solution of LiOH (702 mg, 29.3 mmol) in H₂O (14.7 mL) was added slowly at rt to a solution of cyclopentyl acrylate ester **53m** (1.407 g 8.368 mmol) in MeOH (20 mL). After stirring at rt for 24 h, the reaction mixture was acidified with 10% HCl (15 mL) and the precipitate was collected by filtration. The wet precipitate was dissolved in EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure to provide the acrylic acid **54m** as a white solid (482 mg) that was used in subsequent reactions without further purification. LCMS (ESI) *m/z*: 141.0910 calcd for C₈H₁₂O₂⁺ [M + H]⁺; Found 141.0880. Spectral data for acid **54m** are consistent with those reported previously.²¹

(*E*)-3-Cyclohexylacrylic acid (**54n**)

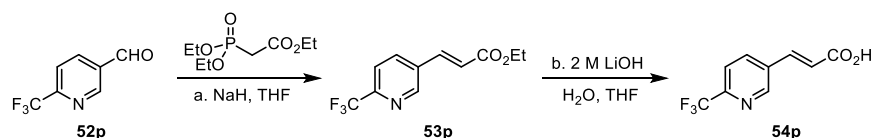


Triethyl phosphonoacetate (856 mg, 3.82 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (155 mg, 3.88 mmol, 60% w/w dispersion in mineral oil) in THF (15 mL). After gas evolution had ceased (~15 min), a solution of cyclopentane carboxaldehyde (283 mg, 2.52 mmol) in THF (5 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (0→40% EtOAc/Hex) to provide ester **53n** (*E/Z* ~96:4) as a colorless oil (305 mg, 1.67 mmol, 66%). ¹H NMR (700 MHz, CDCl₃): δ 6.89 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.74 (dd, *J* = 15.6, 1.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.14–2.07 (m, 1H), 1.78–1.70 (m, 4H), 1.68–1.61 (m, 1H), 1.31–1.22 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.19–1.07 (m, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 167.0, 153.5, 119.4, 60.1, 42.9, 32.4 (2C), 26.0, 25.3 (2C), 14.3. Spectral data for ester **53n** are consistent with those reported previously.²²

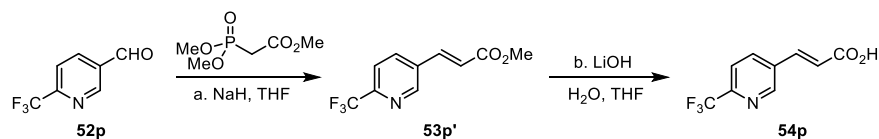
19. Meyers, M. J.; Arhancet, G. B.; Hockerman, S. L.; Chen, X.; Long, S. A.; Mahoney, M. W.; Rico, J. R.; Garland, D. J.; Blinn, J. R.; Collins, J. T.; Yang, S.; Huang, H.-C.; McGee, K. F.; Wendling, J. M.; Dietz, J. D.; Payne, M. A.; Homer, B. L.; Heron, M. I.; Reitz, D. B.; Hu, X. Discovery of (3*S*,3*aR*)- 2-(3-chloro-4-cyanophenyl)-3-cyclopentyl-3,3*a*,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic acid (PF-3882845), an orally efficacious mineralocorticoid receptor (MR) antagonist for hypertension and nephropathy. *J. Med. Chem.* **2010**, *53*, 5979–6002 (doi:10.1021/jm100505n).
20. Heuser, S.; Barrett, D. G.; Berg, M.; Bonnier, B.; Kahl, A.; De La Peunte, M. L.; Oram, N.; Riedl, R.; Roettig, U.; Gil, G. S.; Seger, E.; Steggles, D. J.; Wanner, J.; Weichert, A. G. Synthesis of novel cyclopropylic sulfones and sulfonamides acting as glucokinase activators. *Tetrahedron Lett.* **2006**, *47*, 2675–2678 (doi:10.1016/j.tetlet.2006.02.110).
21. Nishizawa, R.; Nishiyama, T.; Hisaichi, K.; Minamoto, C.; Murota, M.; Takaoka, Y.; Nakai, H.; Tada, H.; Sagawa, K.; Shibayama, S.; Fukushima, D.; Maeda, K.; Mistuya, H. Discovery of 4-[4-({(3*R*)-1-butyl-3-[(*R*)-cyclohexyl(hydroxy)methyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]undec-9-yl}methyl)phenoxy]benzoic acid hydrochloride: A highly potent orally available CCR5 selective antagonist. *Bioorg. Med. Chem.* **2011**, *19*, 4028–4042 (doi:10.1016/j.bmc.2011.05.022).
22. Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruck, M.; McQuade, D. T. A chiral 6-membered *N*-heterocyclic carbene copper(I) complex that induces high stereoselectivity. *Org. Lett.* **2010**, *12*, 5008–5011 (doi:10.1021/ol1021756).

A 2.0 M solution of LiOH (121 mg, 5.06 mmol) in H₂O (2.53 mL) was added slowly at rt to a solution of cyclohexyl acrylate ester **53n** (305 mg 1.67 mmol) in MeOH (20 mL). After stirring at rt for 24 h, the reaction mixture was acidified carefully with 10% HCl (15 mL). The aqueous solution was then extracted with EtOAc (2 × 25 mL) and the organic extracts dried over Na₂SO₄, concentrated under reduced pressure, and subjected to flash chromatography (0→10% MeOH/CH₂Cl₂) to provide the cyclohexyl acrylic acid **54n** as a white amorphous solid (105 mg, 0.681 mmol, 41%). ¹H NMR (700 MHz, CDCl₃): δ 12.5–11.2 (brs, 1H), 7.03 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.77 (dd, *J* = 15.8, 1.4 Hz, 1H), 2.20–2.12 (m, 1H), 1.81–1.73 (m, 4H), 1.70–1.64 (m, 1H), 1.34–1.23 (m, 2H), 1.22–1.11 (m, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 172.9, 157.3, 118.4, 40.7, 31.6 (2C), 26.0, 25.8 (2C). LCMS (ESI) *m/z*: 177.0886 calcd for C₉H₁₄O₂Na⁺ [*M* + Na]⁺; Found 177.0890. Acid **54n** has been reported previously.²¹

(*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylic acid (**54p**)



Triethyl phosphonoacetate (488 mg, 2.179 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (86 mg, 2.15 mmol, 60% w/w dispersion in mineral oil) in THF (5 mL). After gas evolution had ceased (10–15 min), a solution of *E*-3-(2-trifluoromethyl-5-pyridyl)propenal **52p** (251 mg, 1.43 mmol) in THF (5 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), and satd NaCl (25 mL). The organic solution was dried over Na₂SO₄ and concentrated under reduced pressure to provide ester **53p** as an amorphous solid (202 mg) that was used in the subsequent reaction without further purification. *R*_f = 0.52 (30% EtOAc/Hex). A 2.0 M solution of LiOH (71 mg, 2.96 mmol) in H₂O (1.48 mL) was added slowly at rt to a solution of the crude ester **53p** (202 mg, ~0.825 mmol) in MeOH (8 mL) and H₂O (1 mL). After stirring at rt for 24 h, the reaction mixture was acidified with 10% HCl (15 mL). The resulting precipitate was collected by filtration to provide the acid **54p** as an off-white solid (78 mg, 0.358 mmol, 25% over 2 steps). ¹H NMR (700 MHz, acetone-*d*₆): δ 11.70–10.50 (brs, 1H), 9.04 (d, *J* = 1.9 Hz, 1H), 8.40 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 16.2 Hz, 1H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 167.1, 150.7, 148.8 (q, ²*J*_{CF} = 34.5 Hz), 140.3, 137.3, 134.5, 124.1, 122.6 (q, ¹*J*_{CF} = 273.1 Hz), 121.6 (q, ³*J*_{CF} = 3.3 Hz).

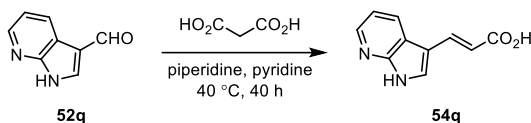


Acid **54p** was also made via the methyl ester **53p'**. Trimethyl phosphonoacetate (1.37 g, 7.50 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (300 mg, 7.50 mmol, 60% w/w dispersion in mineral oil) in THF (50 mL). After gas evolution had ceased (~20 min), a solution of *E*-3-(2-trifluoromethyl-5-pyridyl)propenal **52p** (876 mg, 5.00 mmol) in THF (10 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was transferred to a separatory funnel with satd NaHCO₃ (30 mL). The aqueous suspension was extracted with CH₂Cl₂ (3 ×

30 mL) and the organic extracts washed with satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The crude material was subjected to flash chromatography (0→40% EtOAc/Hex) to provide the methyl ester **53p'** as a white amorphous solid (845 mg, 3.65 mmol, 73%). *R*_f = 0.18 (10% EtOAc/Hex). ¹H NMR (700 MHz, CDCl₃): δ 8.84 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 16.2 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 3.85 (s, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 166.3, 149.6, 149.1 (q, ²*J*_{CF} = 35.3 Hz), 139.5, 135.8, 133.1, 122.6, 121.4 (q, ¹*J*_{CF} = 274.0 Hz), 120.8 (q, ³*J*_{CF} = 2.5 Hz), 52.3. LCMS (ESI) *m/z*: 232.0580 calcd for C₁₀H₉F₃NO₂⁺ [M + H]⁺; Found 232.0586.

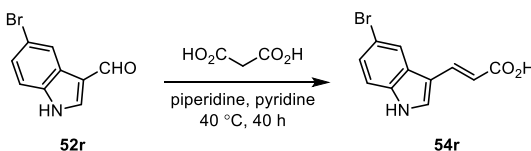
A solution of LiOH (132 mg, 5.51 mmol) in H₂O (10 mL) was added to a solution of the ester **53p'** (638 mg, 2.76 mmol) in THF (10 mL) and stirred at rt for 24 h. The reaction mixture was then acidified to pH ~4 with 10% KHSO₄ (~2–3 mL). The cloudy suspension was extracted with EtOAc (3 × 30 mL), dried over Na₂SO₄, and concentrated in vacuo to provide the acrylic acid **54p** as a white amorphous solid (380 mg, 1.75 mmol). ¹H NMR (700 MHz, DMSO-*d*₆): δ 13.30–12.10 (brs, 1H), 9.07 (d, *J* = 1.7 Hz, 1H), 8.42 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 16.1 Hz, 1H), 6.85 (d, *J* = 16.1 Hz, 1H). ¹³C NMR (175 MHz, DMSO-*d*₆): δ 167.0, 149.8, 146.7 (q, ²*J*_{CF} = 33.7 Hz), 138.7, 136.8, 133.6, 124.3, 121.5 (q, ¹*J*_{CF} = 274.0 Hz), 120.8 (q, ³*J*_{CF} = 2.5 Hz). LCMS (ESI) *m/z*: 218.0423 calcd for C₉H₇F₃NO₂⁺ [M + H]⁺; Found 218.0429.

(*E*)-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylic acid (**54q**)



According to General Procedure D, 3-formyl-1*H*-pyrrolo[2,3-*b*]pyridine **52q** (250 mg, 1.71 mmol) and malonic acid (534 mg, 5.13 mmol) were dissolved in a mixture of pyridine (5 mL) and piperidine (50 μL) and stirred at 40 °C for 40 h. The reaction mixture was cooled to rt, concentrated under reduced pressure, and the resulting residue taken up in 2 M NaOH (25 mL) and washed with EtOAc (25 mL). The aqueous solution was acidified slowly with stirring at 0 °C with 6 M HCl to pH ~2 and the precipitate collected by filtration to provide acid **54q** as a yellow amorphous solid (50 mg, 0.26 mmol, 15%). ¹H NMR (700 MHz, CDCl₃): δ 12.23 (s, 1H), 12.00 (brs, 1H), 8.32–8.28 (m, 2H), 8.04 (d, *J* = 2.5 Hz, 1H), 7.78 (d, *J* = 16.0 Hz, 1H), 7.20 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃): δ 168.4, 149.5, 143.7, 138.0, 131.5, 128.3, 117.3, 117.0, 113.4, 110.5. LCMS (ESI) *m/z*: 189.0659 calculated for C₁₀H₉N₂O₂⁺ [M + H]⁺; Found 189.0662. Spectral data is consistent with data previously reported.²³

(*E*)-3-(5-Bromoindolyl)acrylic acid (**54r**)

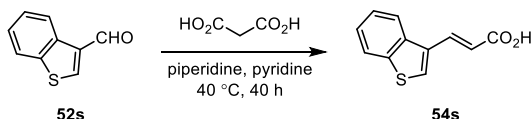


According to General Procedure D, 3-formyl-5-bromoindole **52r** (500 mg, 2.23 mmol) and malonic

23. Minakata, S.; Itoh, S.; Komatsu, M.; Ohshiro, Y. Functionalization of 1*H*-pyrrolo[2,3-*b*]pyridine. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2992–2997 (doi:10.1246/bcsj.65.2992).

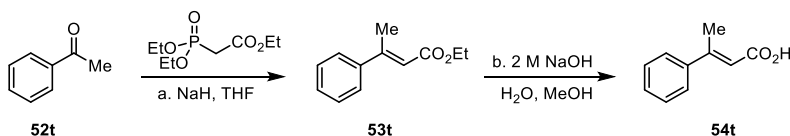
acid (700 mg, 6.73 mmol) were dissolved in a mixture of pyridine (10 mL) and piperidine (100 μ L) and stirred at 40 $^{\circ}$ C for 40 h. The reaction mixture was cooled to rt, concentrated under reduced pressure, and the resulting residue taken up in 2 M NaOH (30 mL) and washed with EtOAc (35 mL). The aqueous solution was acidified slowly with stirring at 0 $^{\circ}$ C with 6 M HCl to pH \sim 2 and the precipitate collected by filtration to provide acid **54r** as a beige amorphous solid (251 mg, 0.942 mmol, 42%). ^1H NMR (700 MHz, DMSO- d_6): δ 11.93 (s, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.95 (s, 1H), 7.76 (d, J = 16.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.32 (dd, J = 8.5, 1.7 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H). ^{13}C NMR (175 MHz, DMSO- d_6): δ 168.6, 137.2, 136.0, 132.0, 126.8, 124.9, 121.9, 114.3, 113.7, 113.4, 111.4. The synthesis of **54r** has been reported previously.²⁴

(*E*)-3-(3-Benzothiophenyl)acrylic acid (**54s**)



As described in General Procedure D, 3-formyl-benzothiophene **52s** (250 mg, 1.54 mmol) and malonic acid (480 mg, 4.61 mmol) were dissolved in a mixture of pyridine (5 mL) and piperidine (50 μ L) and stirred at 40 $^{\circ}$ C for 40 h. The reaction mixture was cooled to rt, concentrated under reduced pressure, and the resulting residue taken up in 2 M NaOH (30 mL) and washed with EtOAc (35 mL). The aqueous solution was acidified slowly with stirring at 0 $^{\circ}$ C with 6 M HCl to pH \sim 2 and the precipitate collected by filtration to provide acid **54s** as a white amorphous solid (226 mg, 1.11 mmol, 72%). ^1H NMR (700 MHz, CDCl₃): δ 12.46 (brs, 1H), 8.40 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.50 (appt, J = 7.5 Hz, 1H), 7.45 (appt, J = 7.2 Hz, 1H), 6.63 (d, J = 16.0 Hz, 1H). ^{13}C NMR (175 MHz, CDCl₃): δ 167.7, 139.9, 136.8, 135.4, 130.9, 129.6, 125.2, 125.0, 123.3, 122.0, 119.7. LCMS (ESI) m/z : 205.0318 calcd for C₁₁H₉O₂S⁺ [M + H]⁺; Found 205.0328. Spectral data for **54s** are consistent with a previous report.²⁵

(*E*)-3-Phenylbut-2-enoic acid (**54t**)^{15,16,26}



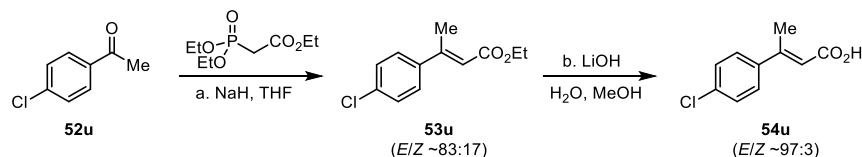
Triethyl phosphonoacetate (4.341 g, 19.36 mmol) was added slowly dropwise at 0 $^{\circ}$ C to a stirring suspension of NaH (728 mg, 18.2 mmol, 60% w/w dispersion in mineral oil) in THF (65 mL). After gas evolution had ceased (\sim 20 min), a solution of acetophenone **52t** (1.551 g, 12.36 mmol) in THF (10 mL)

24. Hawash, M.; Kahraman, D. C.; Cetin-Atalay, R.; Baytas, S. N. Induction of apoptosis in hepatocellular carcinoma cell lines by novel indolylacrylamide derivatives: Synthesis and biological evaluation. *Chem. Biodivers.* **2021**, *18*, e2001037 (doi:10.1002/cbdv.202001037).
25. Liscio, P.; Carotti, A.; Ascitti, S.; Ferri, M.; Pires, M. M.; Valloscuro, S.; Ziff, J.; Clark, N. R.; Macchiarulo, A.; Aaronson, S. A.; Pellicciari, R.; Camaioni, E. Scaffold hopping approach on the route to selective tankyrase inhibitors. *Eur. J. Med. Chem.* **2014**, *87*, 611–623 (doi:10.1016/j.ejmech.2014.10.007).
26. Brégent, T.; Bouillon, J.-P.; Poisson, T. Copper-photocatalyzed *contra*-thermodynamic isomerization of polarized alkenes. *Org. Lett.* **2020**, *22*, 7688–7693 (doi:10.1021/acs.orglett.0c02894).

was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→40% EtOAc/Hex) provided the ester **53t** as a pale yellow oil that was used in the next reaction without further purification. *R*_f = 0.39 (10% EtOAc/Hex).

A 2.0 M solution of NaOH (15 mL, 30 mmol) was added to a solution of the crude ester **53t** in MeOH (10 mL) and stirred at rt for 24 h. The reaction mixture was then acidified to pH ~2 with 10% HCl and the resulting precipitate was collected by filtration. The wet solid was dissolved in satd Na₂CO₃ (15 mL) and washed with CH₂Cl₂ (2 × 15 mL) before the aqueous phase was acidified to pH ~2 with 10% HCl and extracted with Et₂O (3 × 30 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to provide acid **54t** as a white amorphous solid (1.74 g, 10.7 mmol, 83% over 2 steps). ¹H NMR (700 MHz, CDCl₃): δ 12.5–11.0 (brs, 1H), 7.53–7.48 (m, 2H), 7.43–7.37 (m, 3H), 6.19 (s, 1H), 2.62 (s, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 172.5, 158.9, 142.2, 129.5, 128.8 (2C), 126.6 (2C), 116.6, 18.5. LCMS (ESI) *m/z*: 185.0573 calcd for C₁₀H₁₀O₂Na⁺ [M + Na]⁺; Found 185.0566.

(*E*)-3-(4-Chlorophenyl)but-2-enoic acid (**54u**)

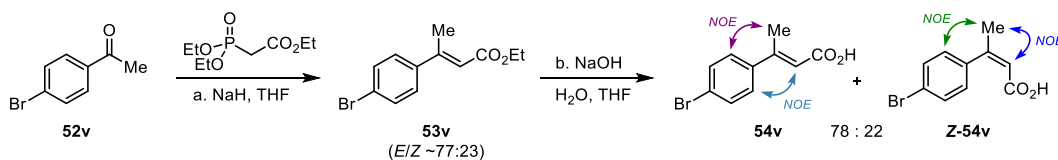


Triethyl phosphonoacetate (2.427 g, 10.83 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (454 mg, 11.35 mmol, 60% w/w dispersion in mineral oil) in THF (50 mL). After gas evolution had ceased (~20 min), a solution of 4-chloroacetophenone **52u** (1.156 g, 7.479 mmol) in THF (10 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→20% MeOH/CH₂Cl₂) provided the ester **53u** (*E/Z* ~83:17) as an oily solid (749 mg, 3.33 mmol, 45%). ¹H NMR (700 MHz, CDCl₃): δ 7.39 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.10 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 166.7, 154.0, 140.6, 135.0, 128.7 (2C), 127.7 (2C), 117.6, 60.0, 17.8, 14.4.

The ethyl ester **53u** (749 mg 3.33 mmol) was stirred with MeOH (10 mL) and 2 M LiOH (279 g, 11.6 mmol) at rt for 24 h. The reaction was acidified with 10% HCl and the precipitate collected by filtration to provide acid **54u** as an off-white solid (63 mg, 0.32 mmol, 9%). ¹H NMR (700 MHz, acetone-*d*₆): δ 10.90–10.48 (brs, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.18 (q, *J* = 1.3 Hz, 1H), 2.55 (d, *J* = 1.3 Hz, 3H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 167.7, 154.7, 141.7, 135.3, 129.5 (2C), 128.9 (2C), 118.2, 17.6. LCMS (ESI) *m/z*: 219.0183 calcd for C₁₀H₉³⁵ClO₂Na⁺ [M + Na]⁺; Found 219.0181. Spectral data for ester **53u** and acid **54u** are consistent with those reported previously.²⁷

27. Metternich, J. B.; Gilmour, R. A bio-inspired, catalytic *E*→*Z* isomerization of activated olefins. *J. Am. Chem. Soc.* **2015**, *137*, 11254–11257 (doi:10.1021/jacs.5b07136).

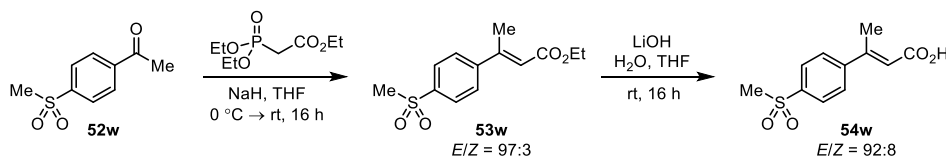
(*E*)-3-(4-Bromophenyl)but-2-enoic acid (**54v**)



Triethyl phosphonoacetate (1.68 g, 7.50 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (300 mg, 7.50 mmol, 60% w/w dispersion in mineral oil) in THF (50 mL). After gas evolution had ceased (~20 min), a solution of *p*-bromoacetophenone **52v** (1.03 g, 5.19 mmol) in THF (10 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→20% EtOAc/Hex) provided the ester **53v** as a mixture of *E/Z* isomers (77:23) as a pale yellow oil (971 mg, 3.61 mmol, 69%). *E/Z* stereochemical assignments were aided by NOESY NMR experiments (page S194). **53v** ¹H NMR (700 MHz, CDCl₃): δ 7.47 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.10 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **Z-53v** ¹H NMR (700 MHz, CDCl₃): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 5.91 (s, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). The syntheses of **53v** and **Z-53v** have been reported previously.^{26,27}

Ethyl ester **53v** (819 mg 3.04 mmol, *E/Z* ~77:23) was stirred with MeOH (10 mL) and a 2 M solution of LiOH (255 mg, 10.7 mmol) in H₂O (5.3 mL) at rt for 24 h. The reaction was then acidified with 10% HCl and the precipitate collected by filtration. The solid was dissolved in EtOAc (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→20% CH₂Cl₂/MeOH) provided the acids **54v** and **Z-54v** (~78:22) as a white solid (497 mg, 2.07 mmol, 30%). **54v** (*E* isomer). ¹H NMR (700 MHz, acetone-*d*₆): δ 10.91–10.28 (brs, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.19 (q, *J* = 1.2 Hz, 1H), 2.54 (d, *J* = 1.2 Hz, 3H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 167.7, 154.8, 142.1, 132.5 (2C), 129.1 (2C), 123.5, 118.3, 17.6. **Z-54v**. ¹H NMR (700 MHz, acetone-*d*₆): δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.97 (q, *J* = 1.4 Hz, 1H), 2.17 (d, *J* = 1.4 Hz, 1H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 166.6, 154.8, 141.1, 131.6 (2C), 130.1 (2C), 121.9, 119.0, 27.0. LCMS (ESI) *m/z*: 238.9713 calcd for C₁₀H₈⁷⁹BrO₂[−] [M − H][−]; Found 238.9710.

(*E*)-3-(4-Methanesulfonylphenyl)but-2-enoic acid (**54w**)



According to General Procedure D, triethyl phosphonoacetate (1.55 g, 6.91 mmol) was added slowly dropwise at 0 °C to a stirring suspension of NaH (282 mg, 7.05 mmol, 60% w/w dispersion in mineral oil) in THF (50 mL). After gas evolution had ceased (~20 min), a solution of 4-methanesulfonylacetophenone **52w** (913 mg, 4.61 mmol) in THF (50 mL) was added slowly at 0 °C and allowed to warm to rt. After stirring for 24 h at rt, the reaction mixture was diluted with EtOAc (25 mL) and washed with satd Na₂CO₃ (25 mL), satd aq. NH₄Cl (25 mL), satd NaCl (25 mL), dried over Na₂SO₄, and concentrated under

reduced pressure. Flash chromatography (0→20% EtOAc/Hex) provided the ester **53v** (*E/Z* ~97:3) as a pale amber oil (553 mg, 2.06 mmol, 49%). ¹H NMR (700 MHz, CDCl₃): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 6.12 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.03 (s, 3H), 2.53 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (175 MHz, CDCl₃): δ 166.2, 153.1, 147.7, 140.6, 127.7 (2C), 127.3 (2C), 119.8, 60.2, 44.5, 18.0, 14.3. Spectral data are consistent with previously reported data for ester **53w**.²⁸

Ethyl ester **53w** (553 mg, 2.06 mmol) was stirred with MeOH (10 mL) and a 2 M solution of LiOH (177 mg, 7.38 mmol) in H₂O (3.7 mL) at rt for 24 h. The reaction was then acidified with 10% HCl and the precipitate collected by filtration. The solid was dissolved in EtOAc (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Flash chromatography (0→20% CH₂Cl₂/MeOH) provided acid **54w** (*E/Z* ~92:8) as a pale yellow solid (241 mg, 1.01 mmol, 49%). ¹H NMR (700 MHz, acetone-*d*₆): δ 10.98–10.66 (brs, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 3.15 (s, 3H), 2.59 (s, 3H). ¹³C NMR (175 MHz, acetone-*d*₆): δ 167.4, 154.3, 148.1, 142.4, 128.5 (2C), 128.1 (2C), 120.2, 44.2, 17.8. LCMS (ESI) *m/z*: 263.0349 calcd for C₁₁H₁₂O₄SNa⁺ [*M* + Na]⁺; Found 263.0360.

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28. Shevlin, M.; Friedfeld, M. R.; Sheng, H.; Pierson, N. A.; Hoyt, J. M.; Campeau, L.-C.; Chirik, P. J. Nickel-catalyzed asymmetric alkene hydrogenation of α,β-unsaturated esters: High-throughput experimentation-enabled reaction discovery, optimization, and mechanistic elucidation. *J. Am. Chem. Soc.* **2016**, *138*, 3562–3569 (doi:10.1021/jacs.6b00519).

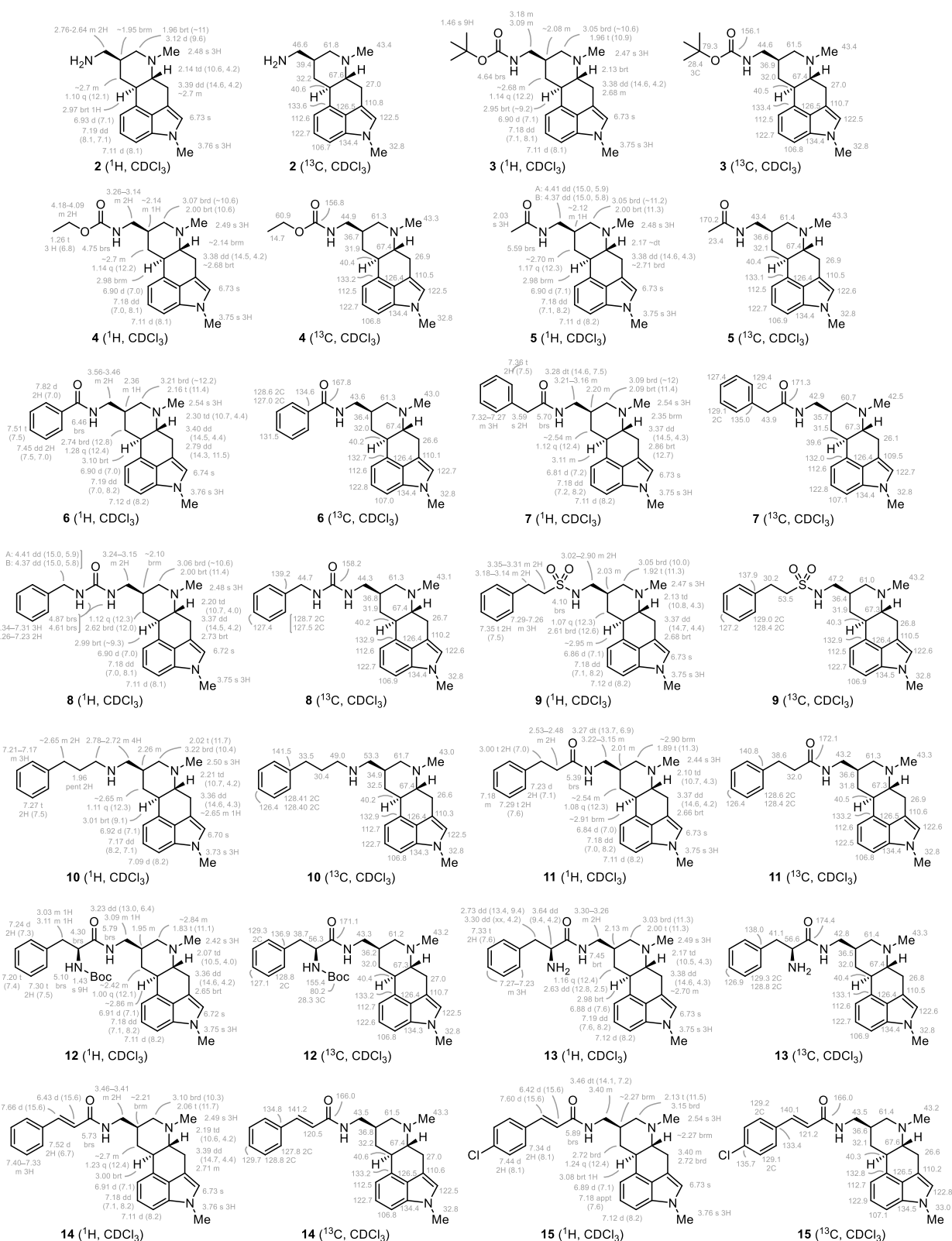


Figure S4. NMR assignments for metergoline analogues and synthetic precursors.

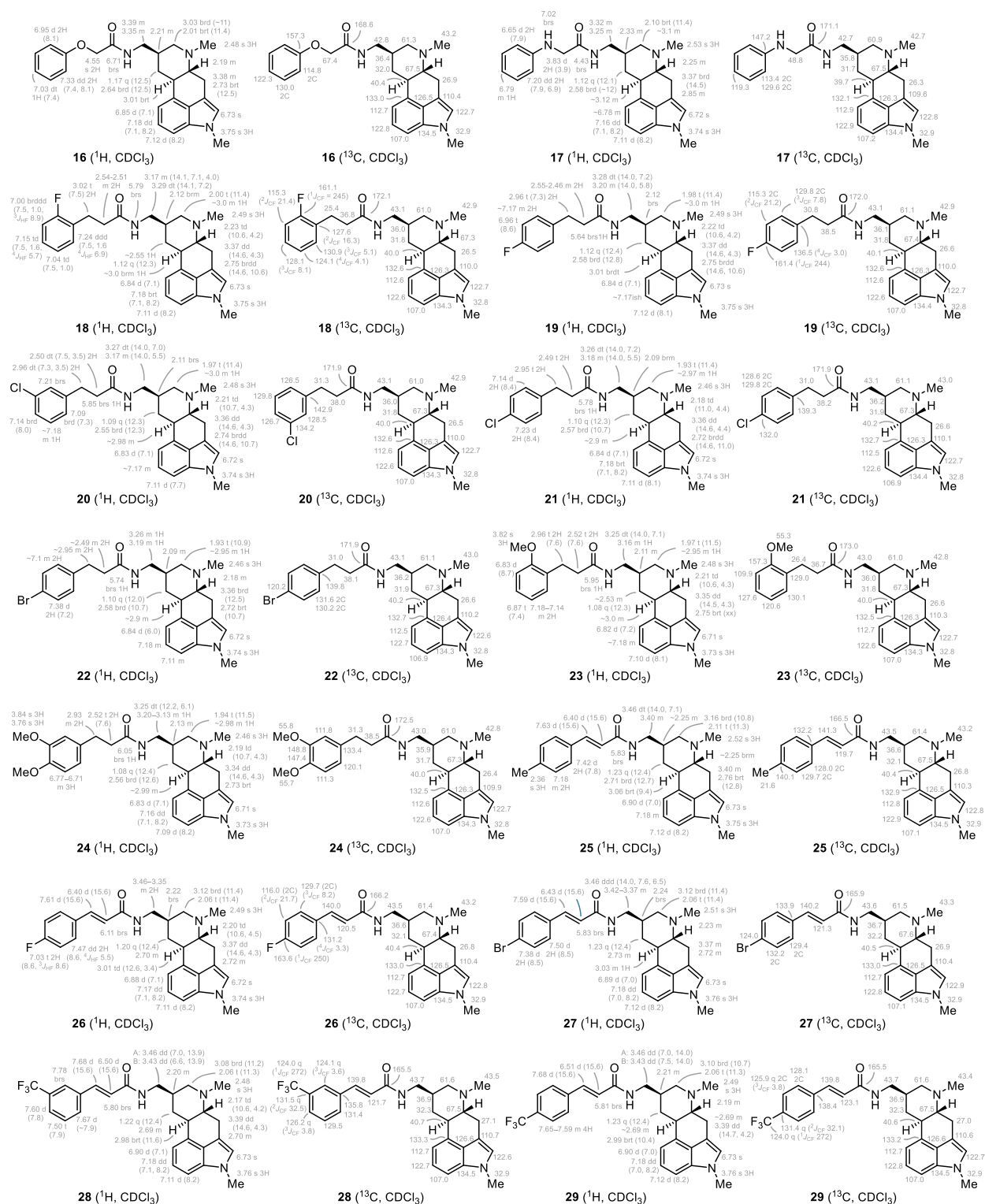


Figure S4. Continued.

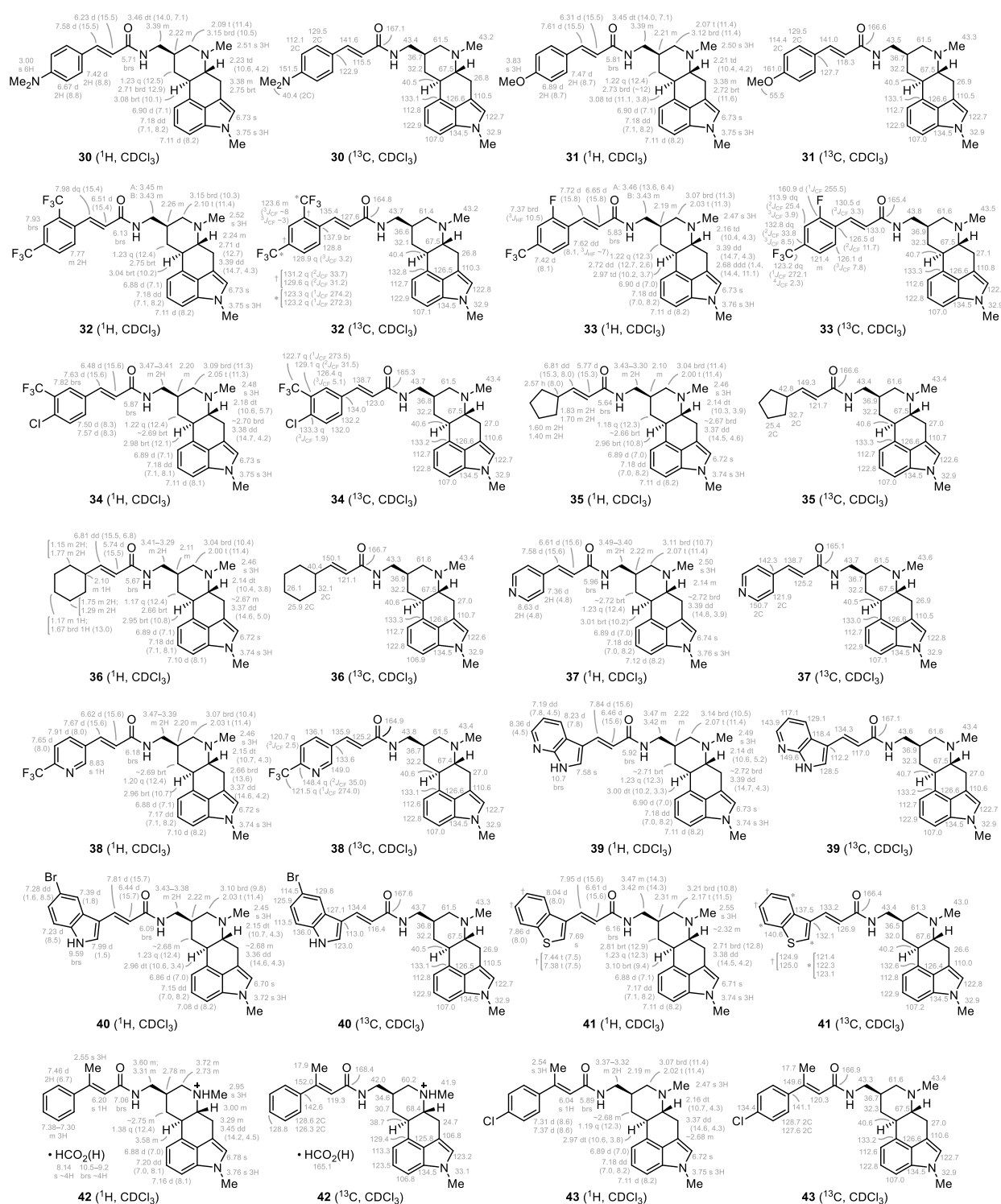
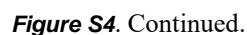
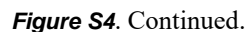


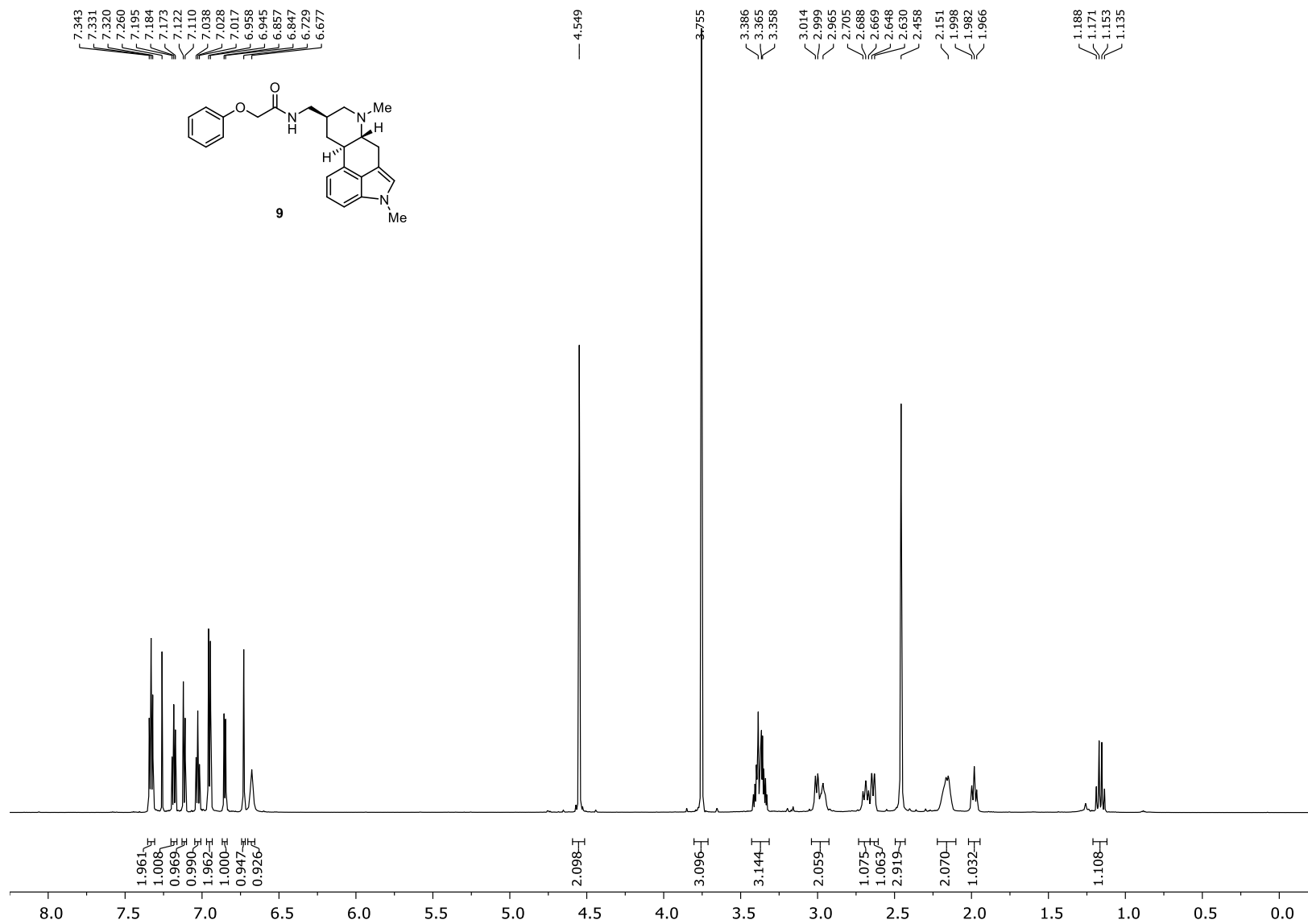
Figure S4. Continued.



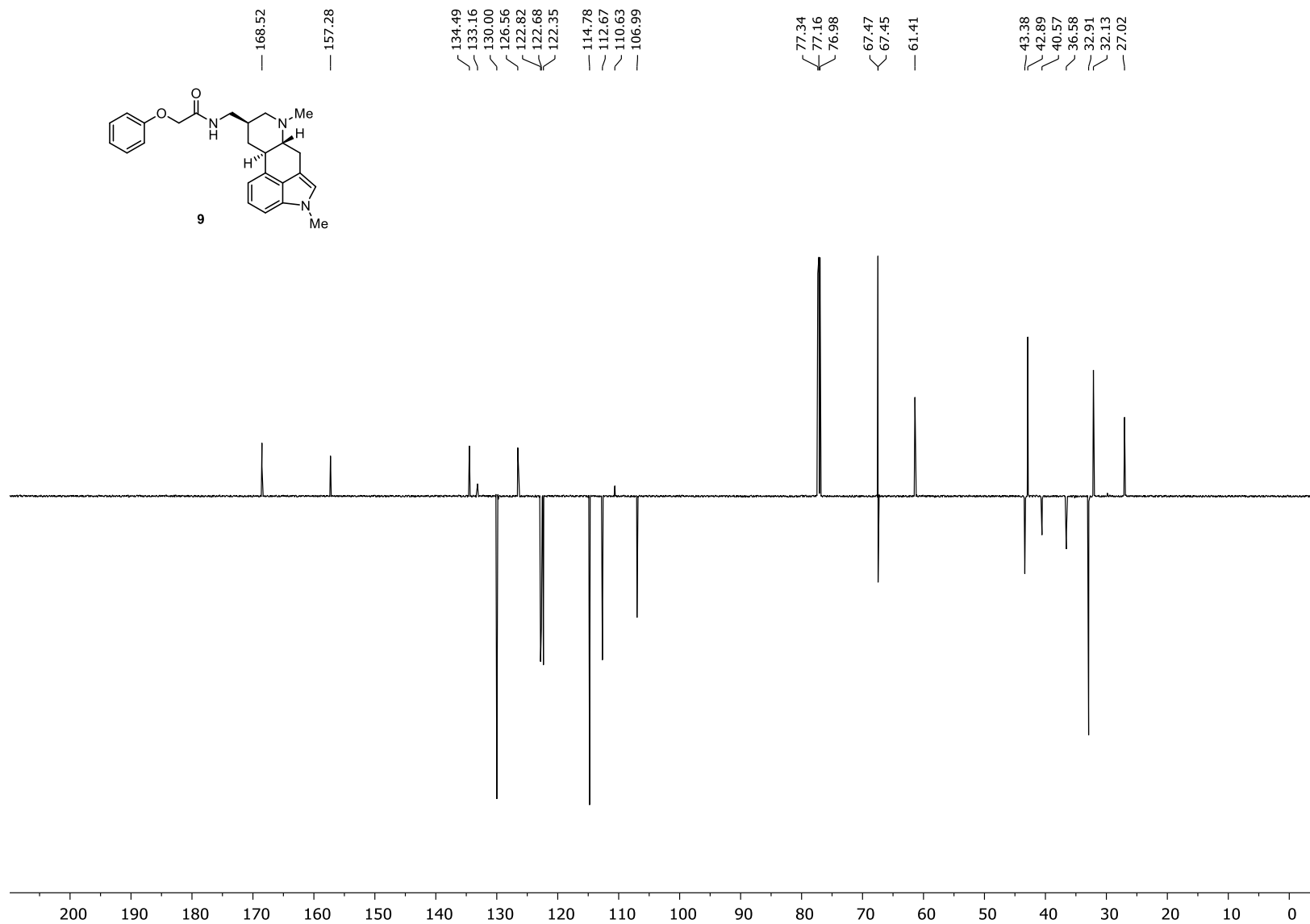


^1H and ^{13}C NMR Spectra

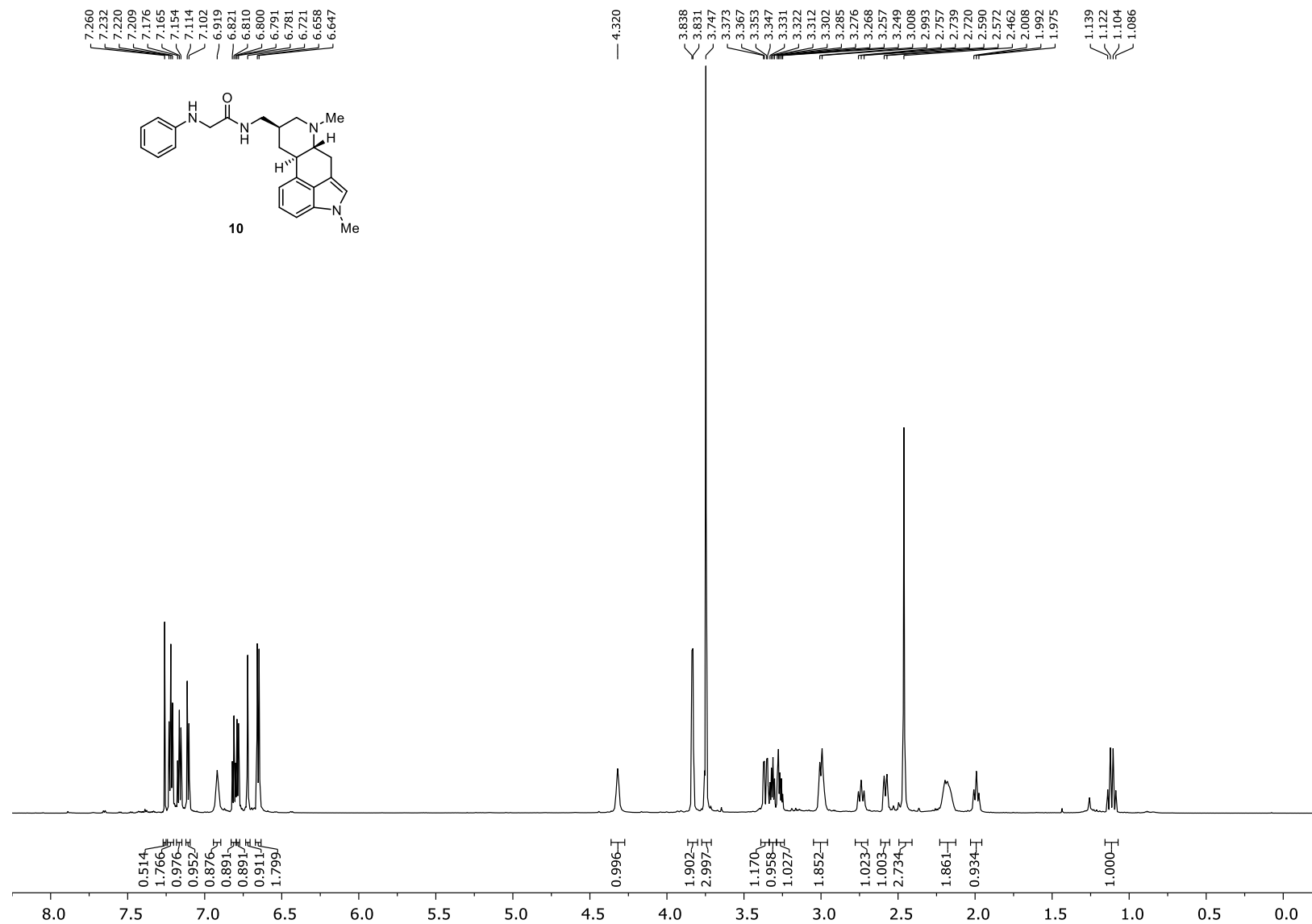
N-(Phenoxyacetyl) ergoline derivative (**9**) (^1H NMR; 700 MHz; CDCl_3)



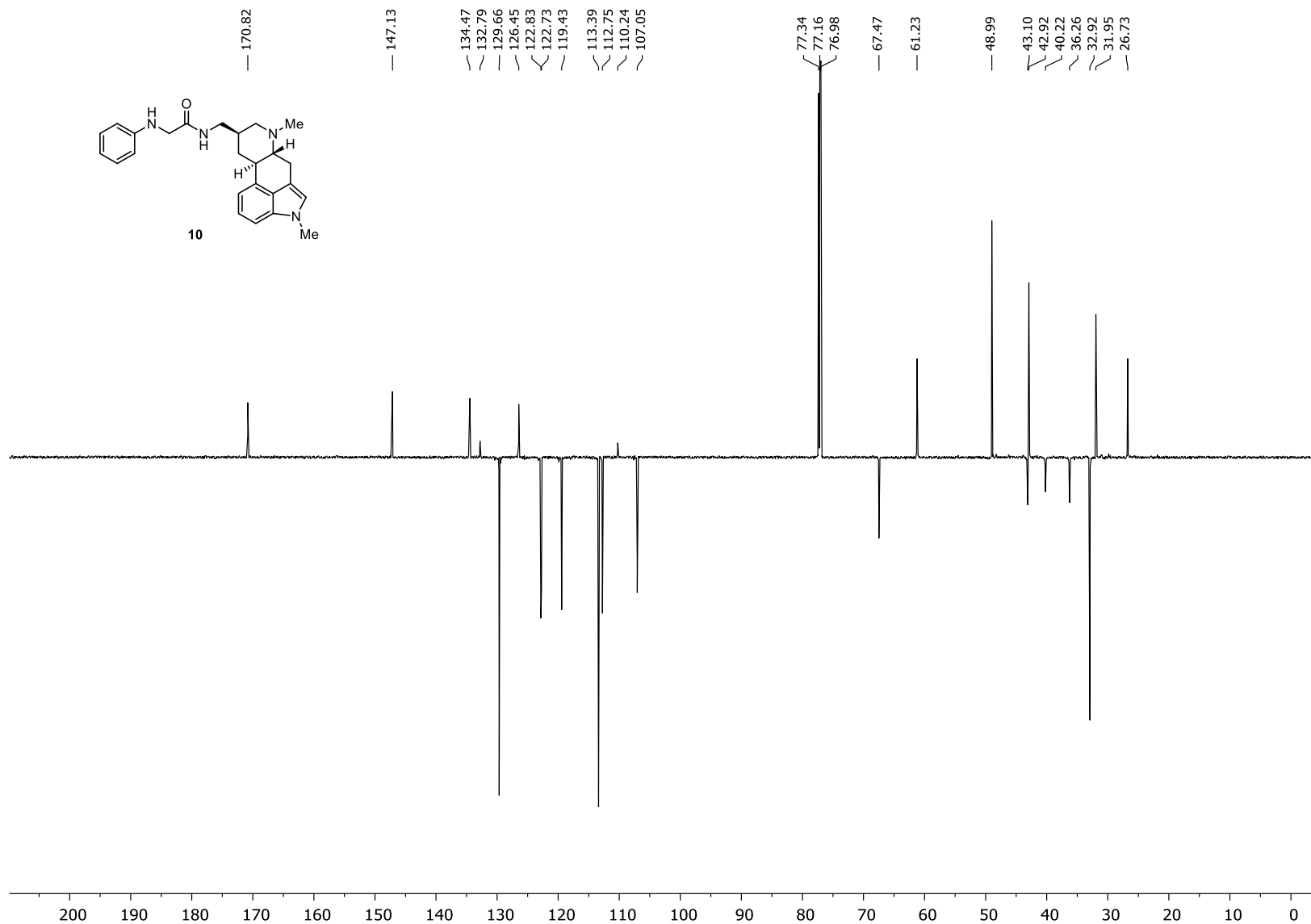
N-(Phenoxyacetyl) ergoline derivative (**9**) (^{13}C NMR; 175 MHz; CDCl_3)



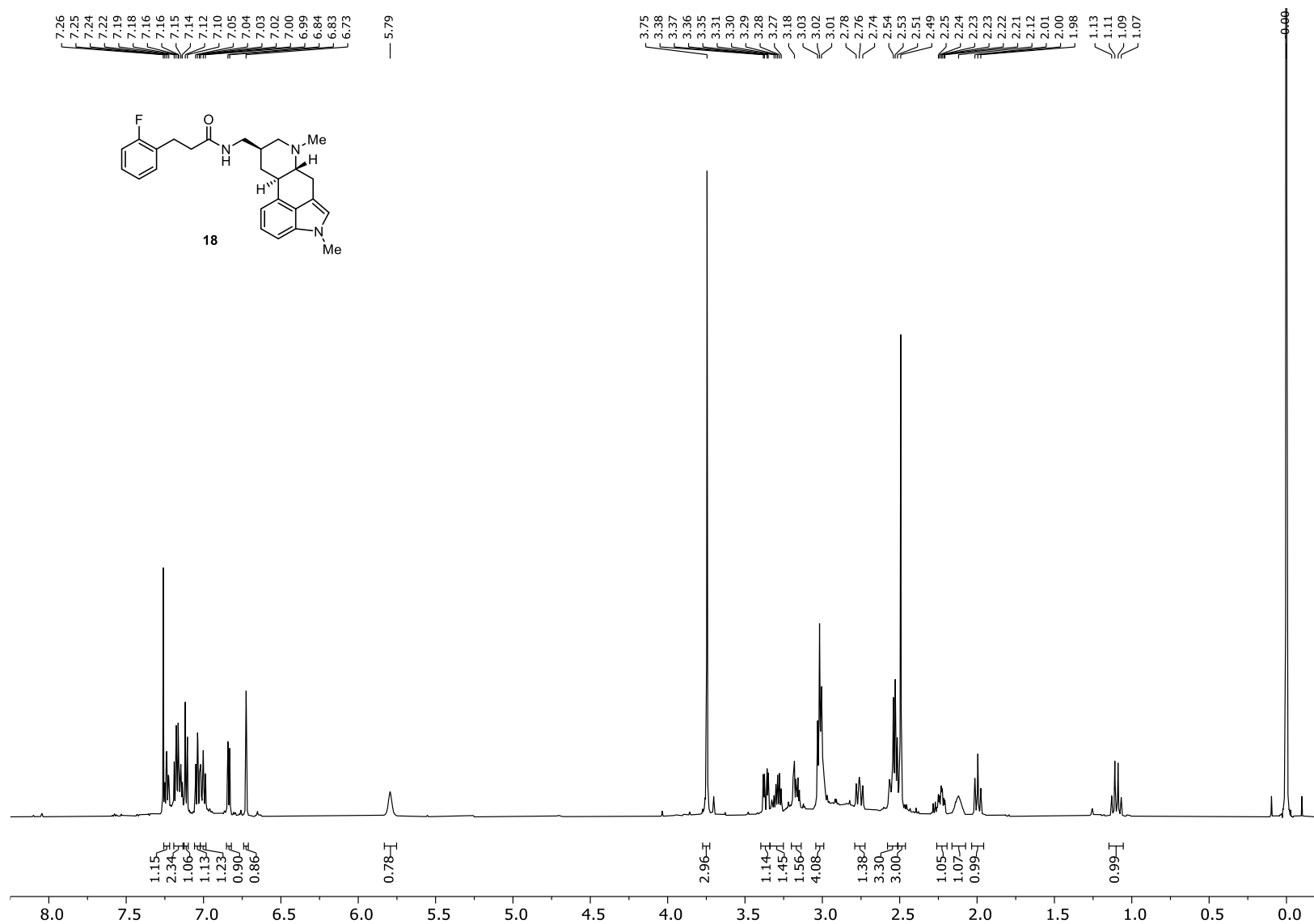
N-(*N*-Phenylglycyl) ergoline derivative (**10**) (^1H NMR; 700 MHz; CDCl_3)



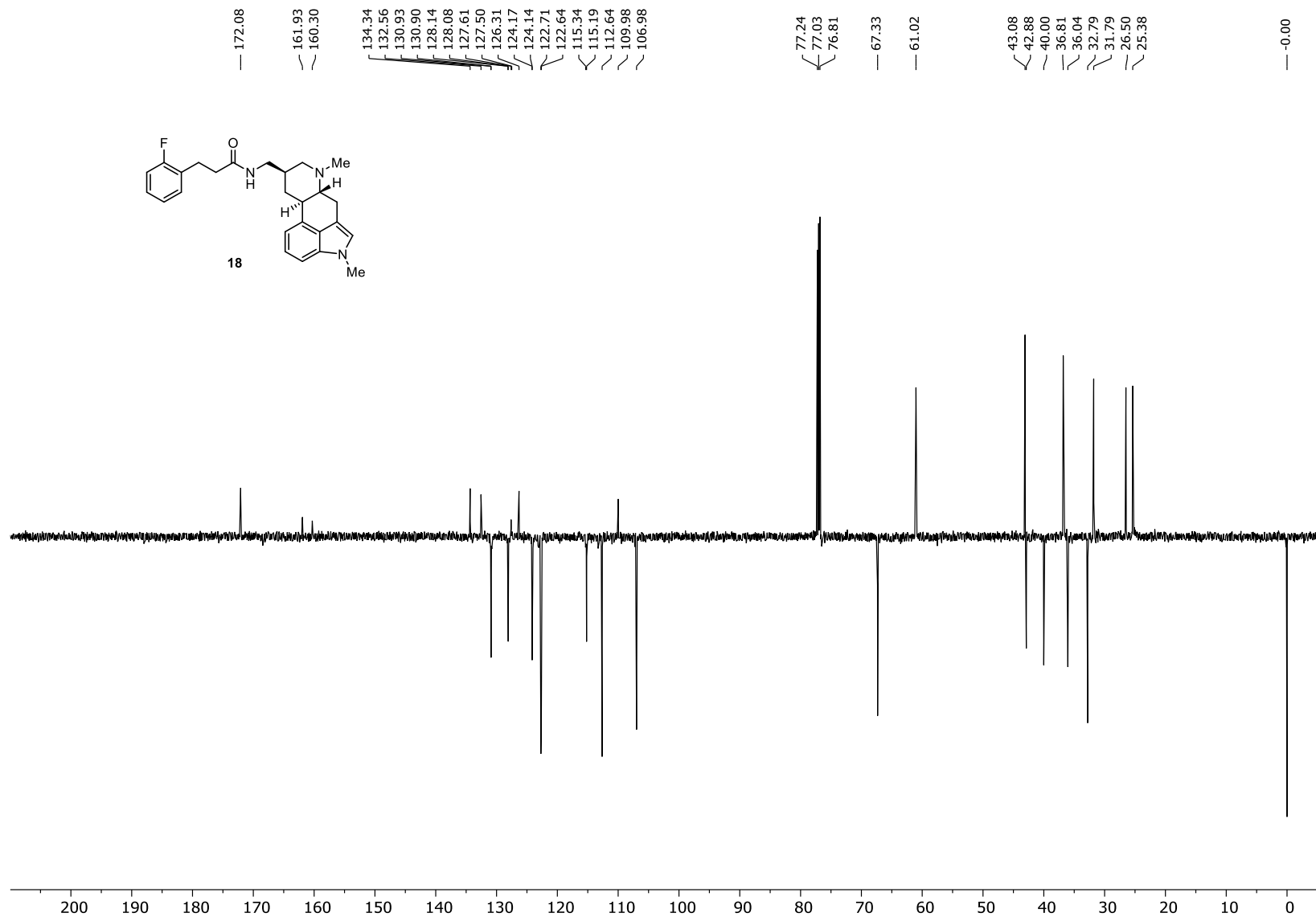
N-(*N*-Phenylglycyl) ergoline derivative (**10**) (^{13}C NMR; 175 MHz; CDCl_3)



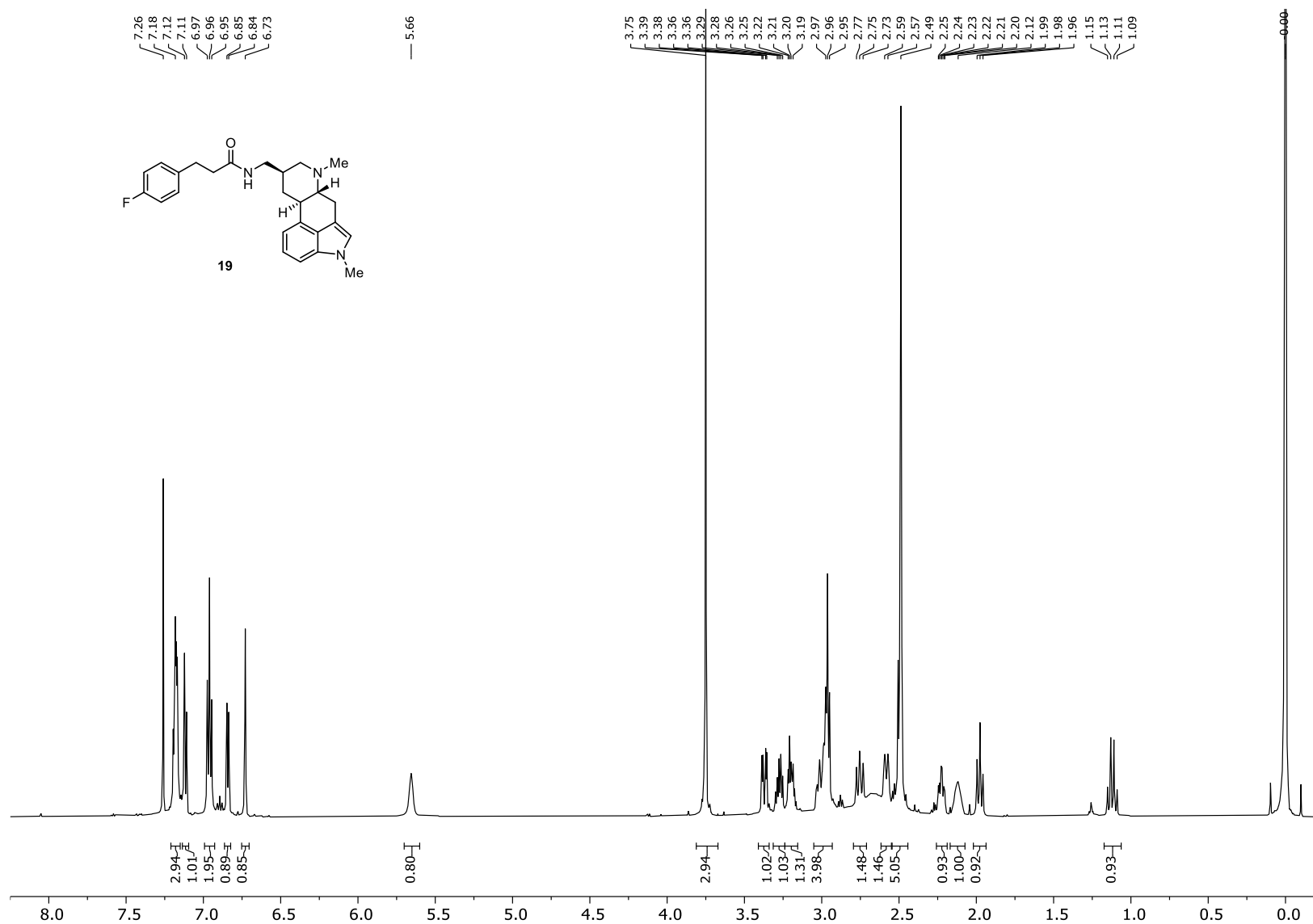
N-(2-Fluoro-hydrocinnamoyl) ergoline derivative (**18**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



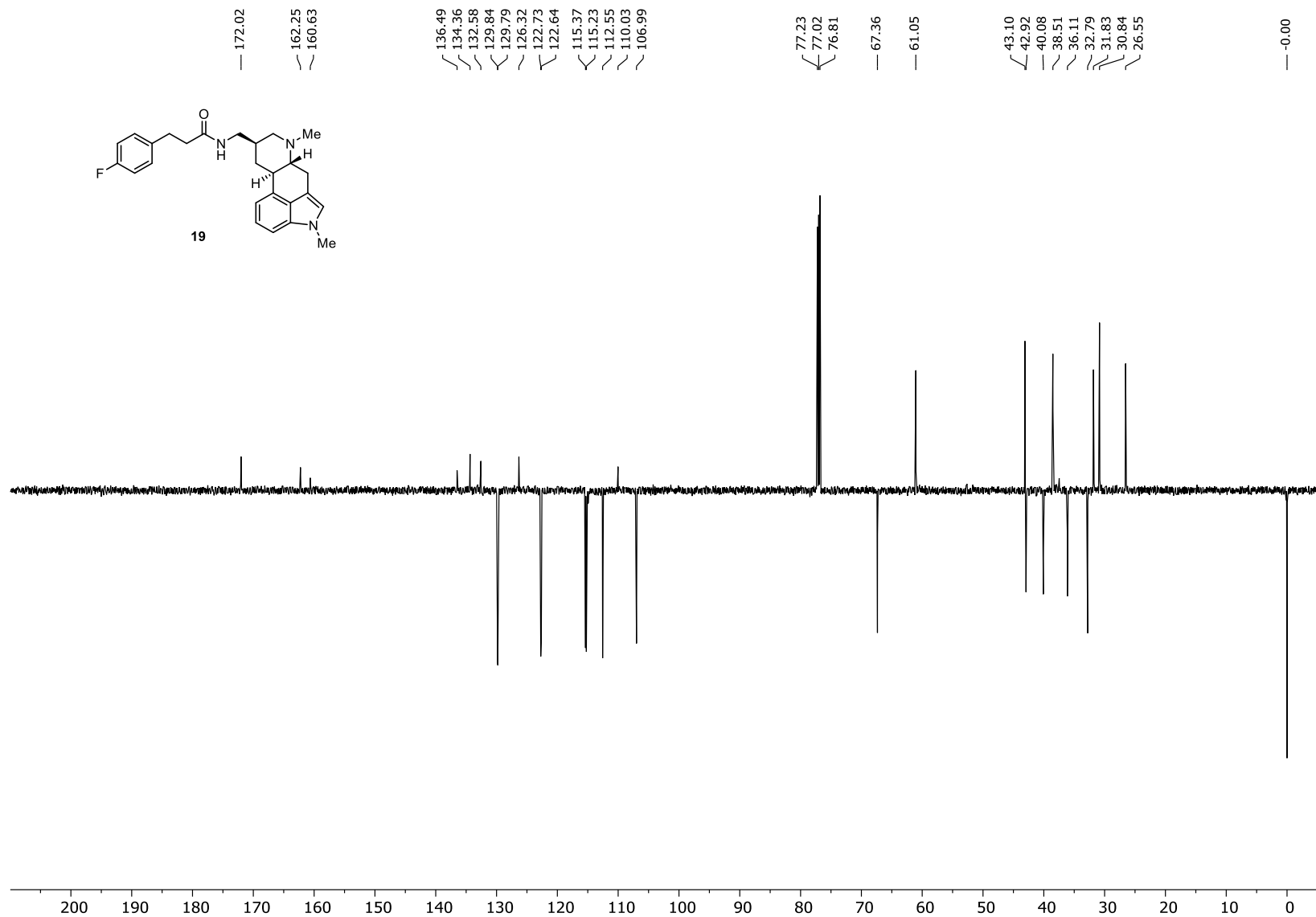
N-(2-Fluoro-hydrocinnamoyl) ergoline derivative (**18**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



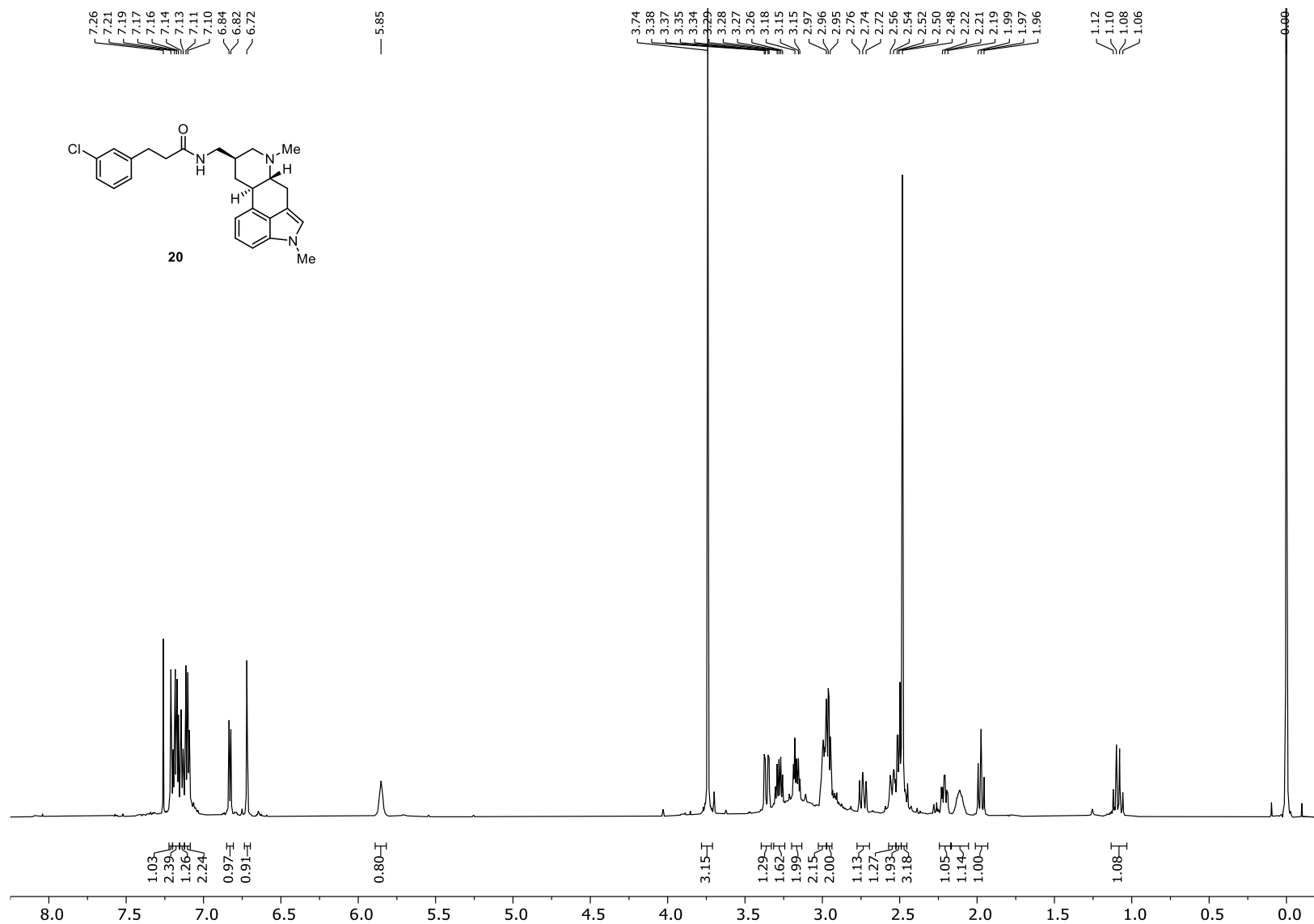
N-(4-Fluoro-hydrocinnamoyl) ergoline derivative (**19**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



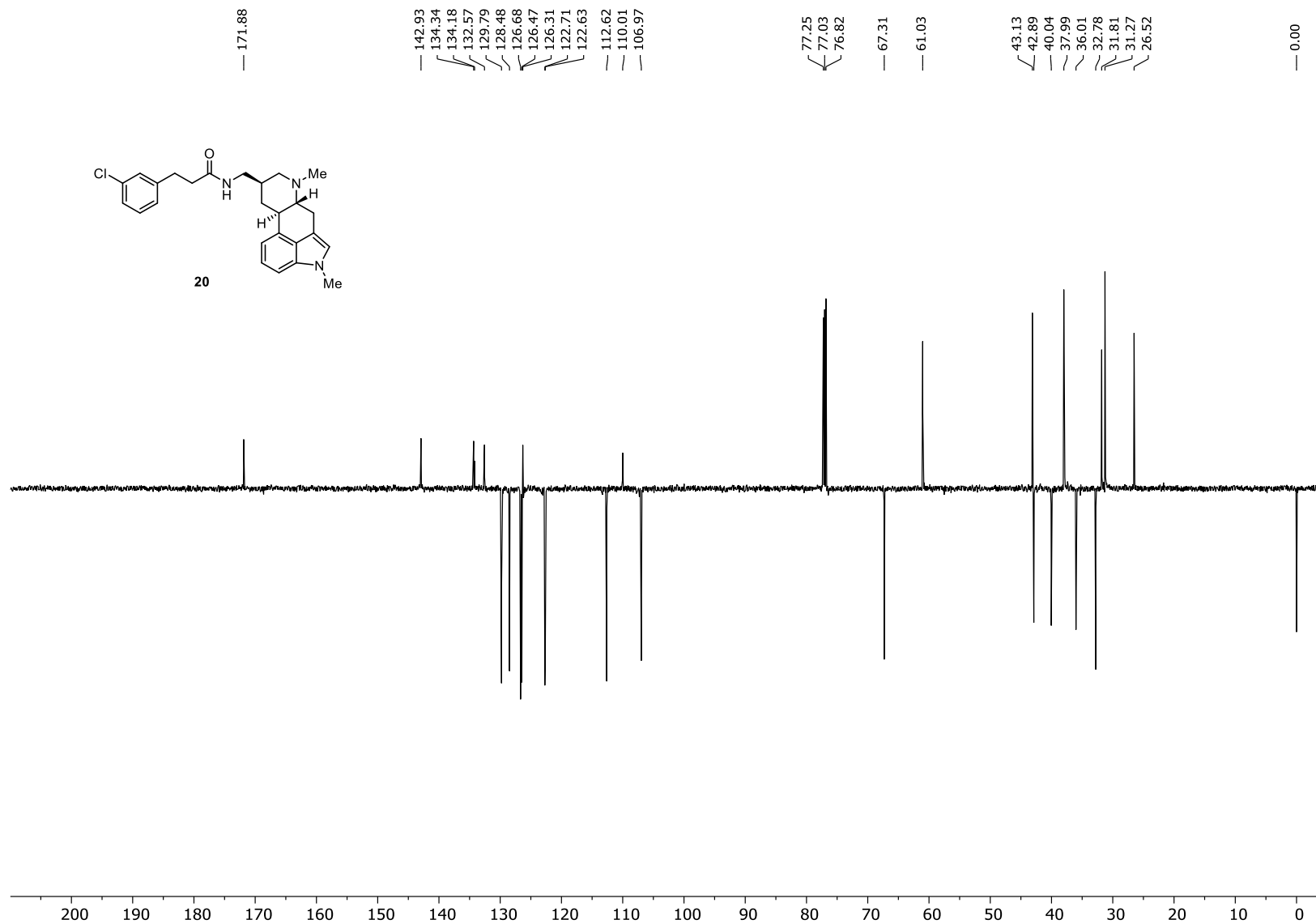
N-(4-Fluoro-hydrocinnamoyl) ergoline derivative (**19**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



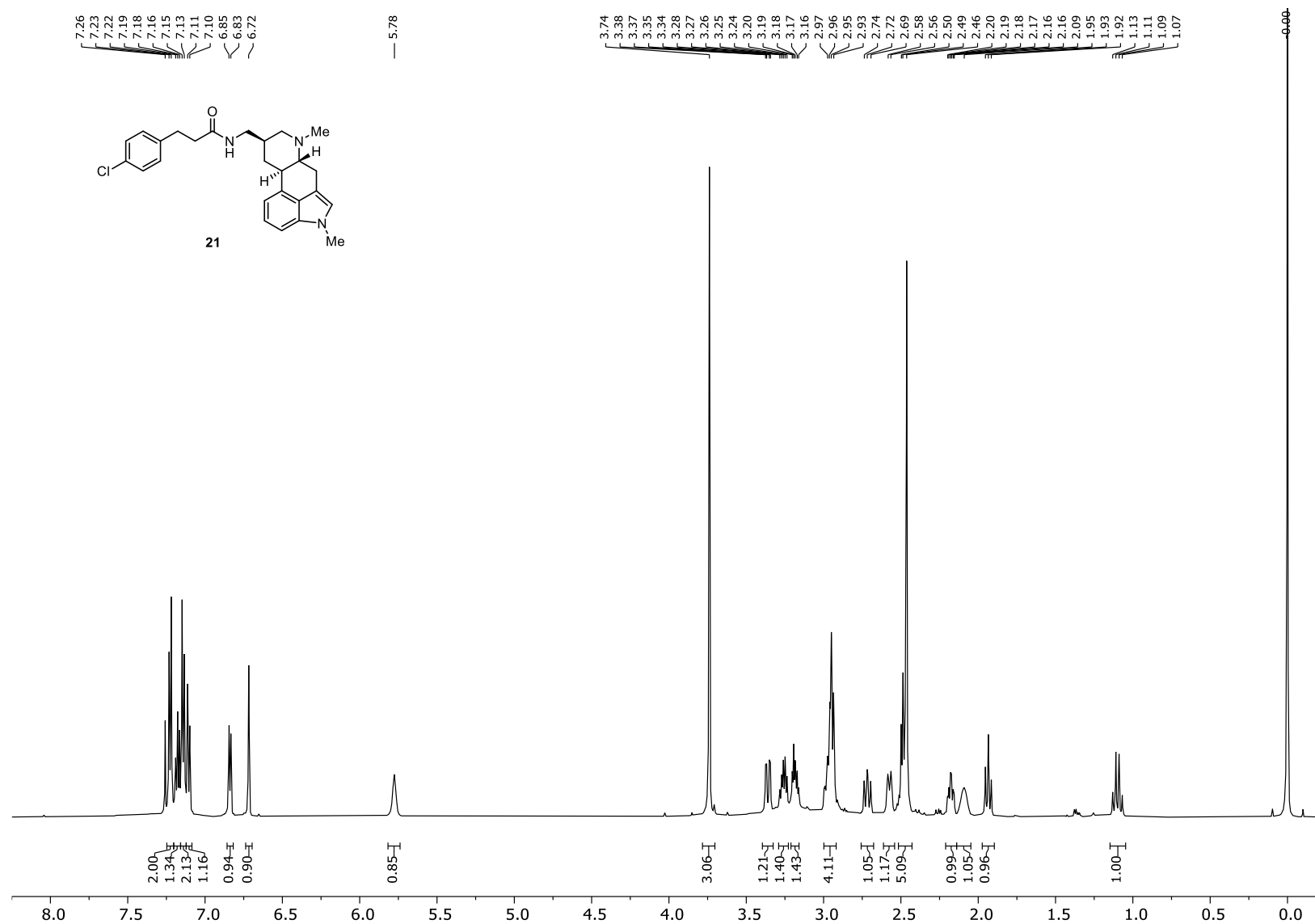
N-(3-Chloro-hydrocinnamoyl) ergoline derivative (**20**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



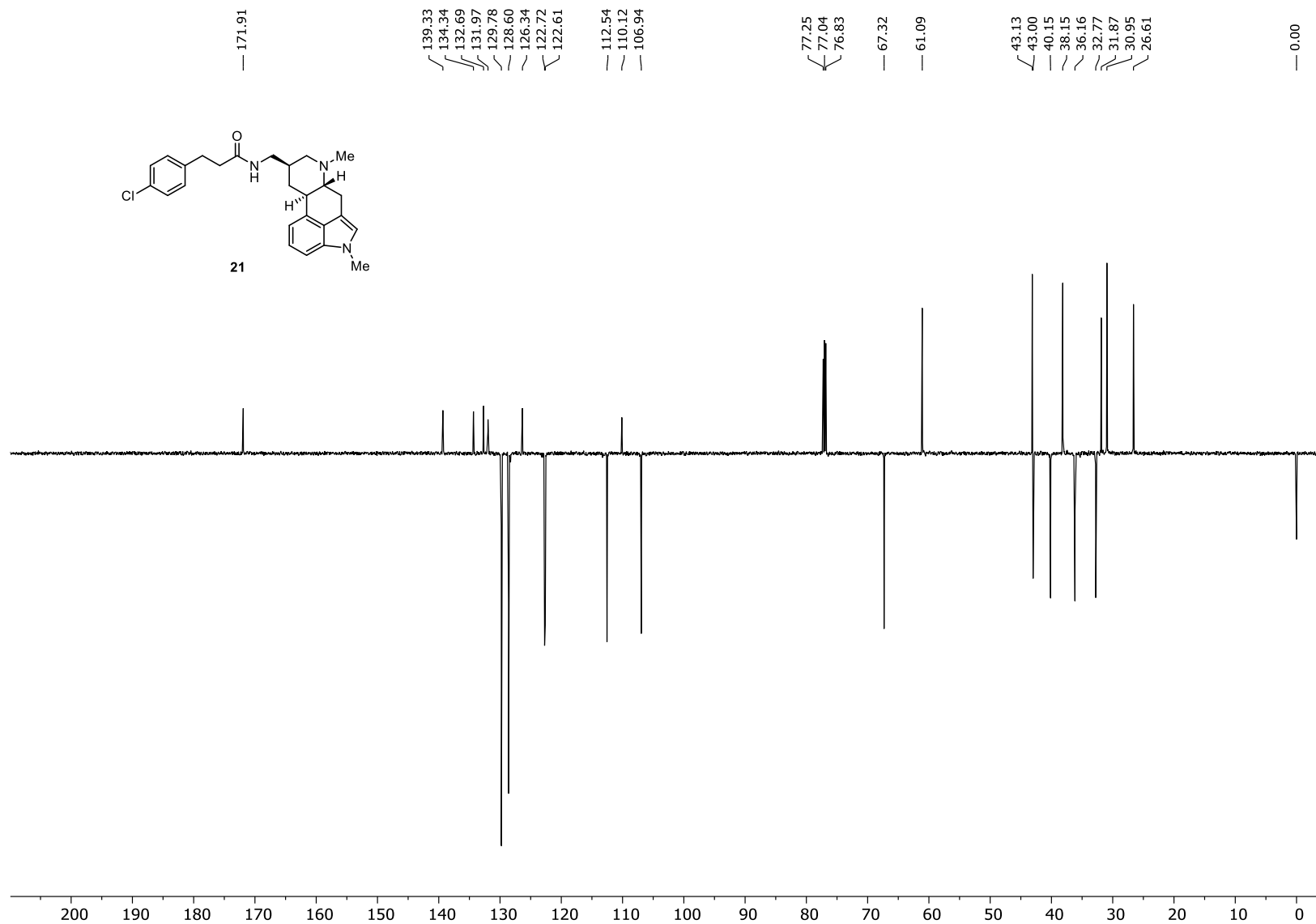
N-(3-Chloro-hydrocinnamoyl) ergoline derivative (**20**) (^{13}C NMR; 150 MHz; CDCl_3)



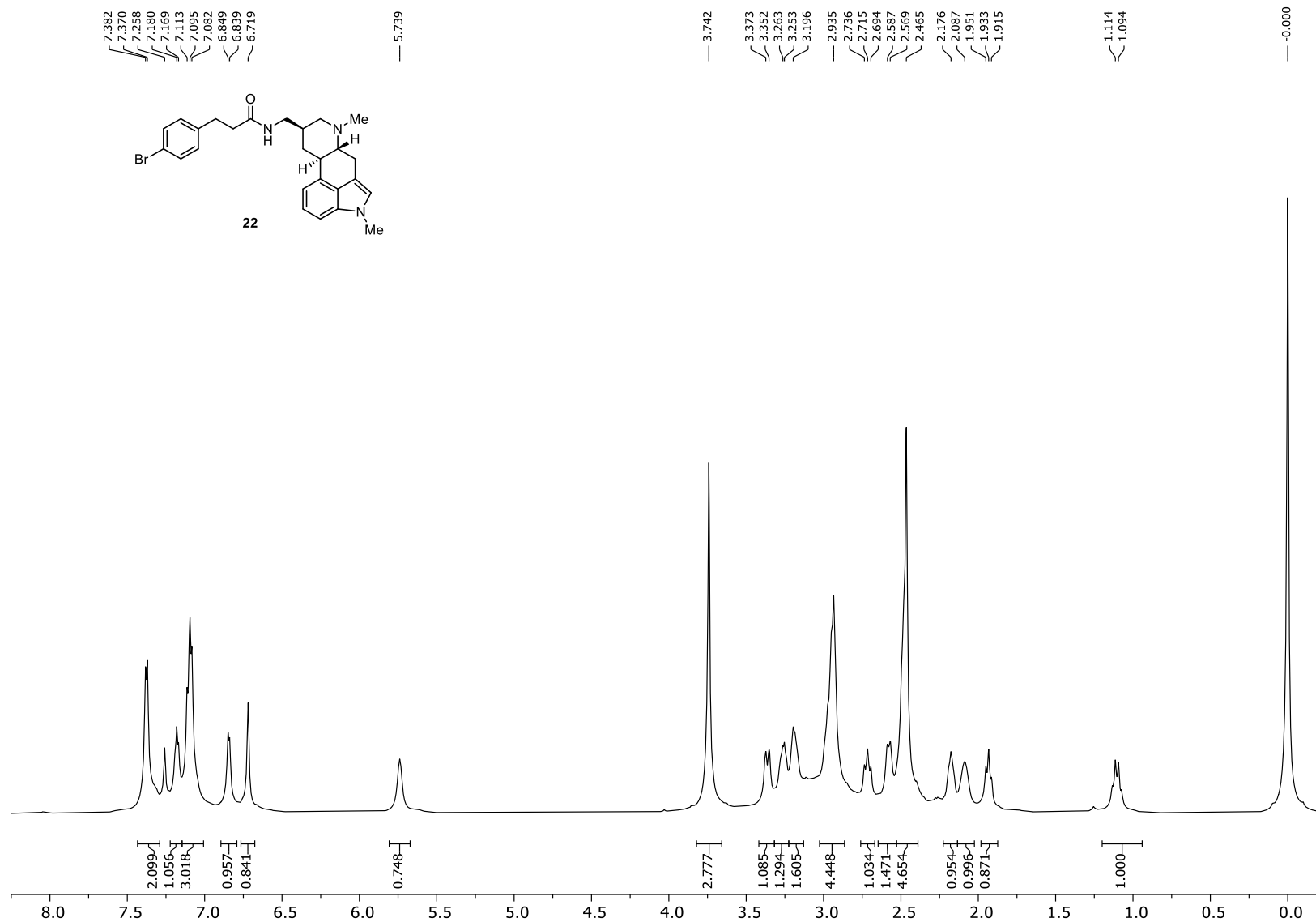
N-(4-Chloro-hydrocinnamoyl) ergoline derivative (**21**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



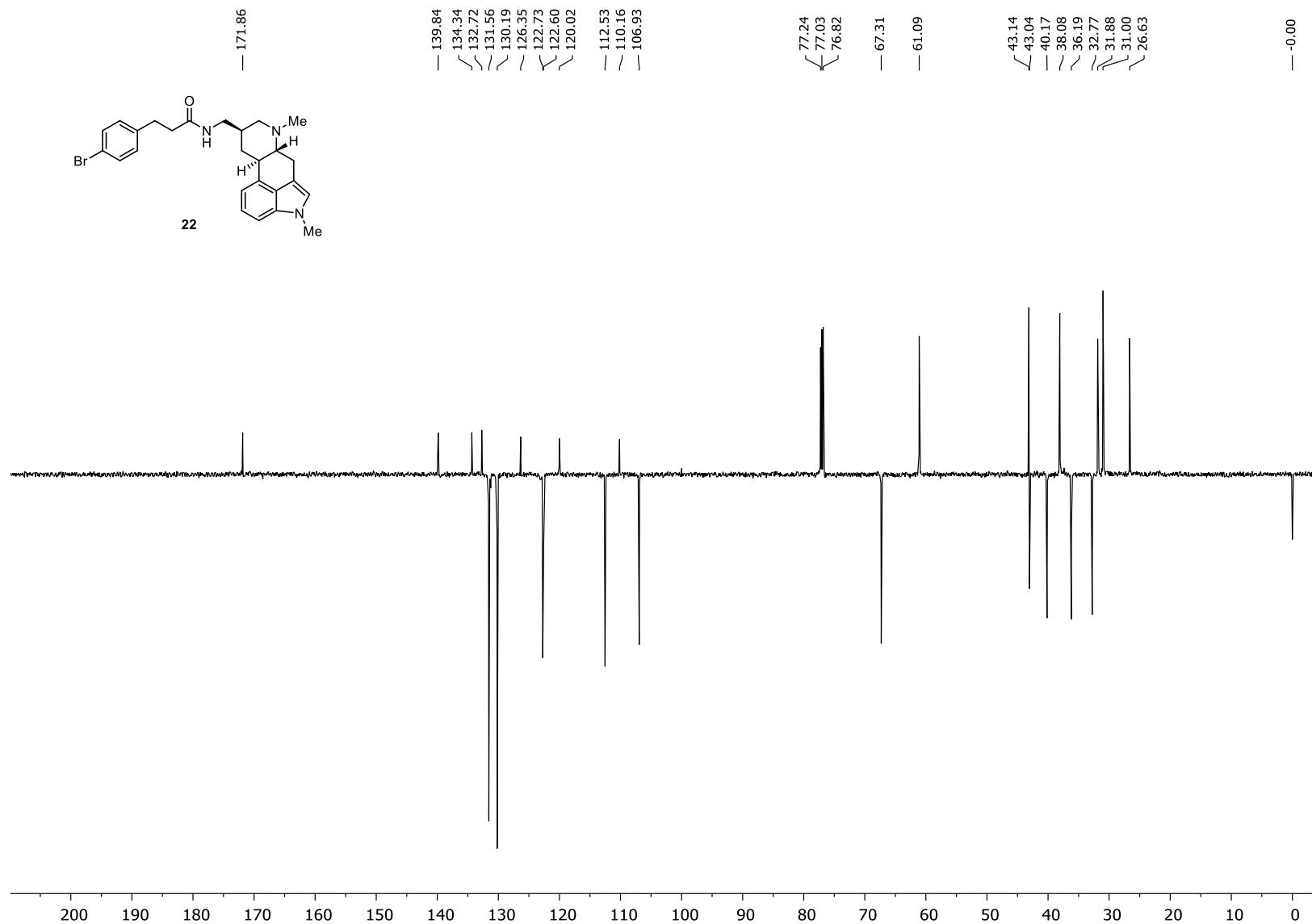
N-(4-Chloro-hydrocinnamoyl) ergoline derivative (**21**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



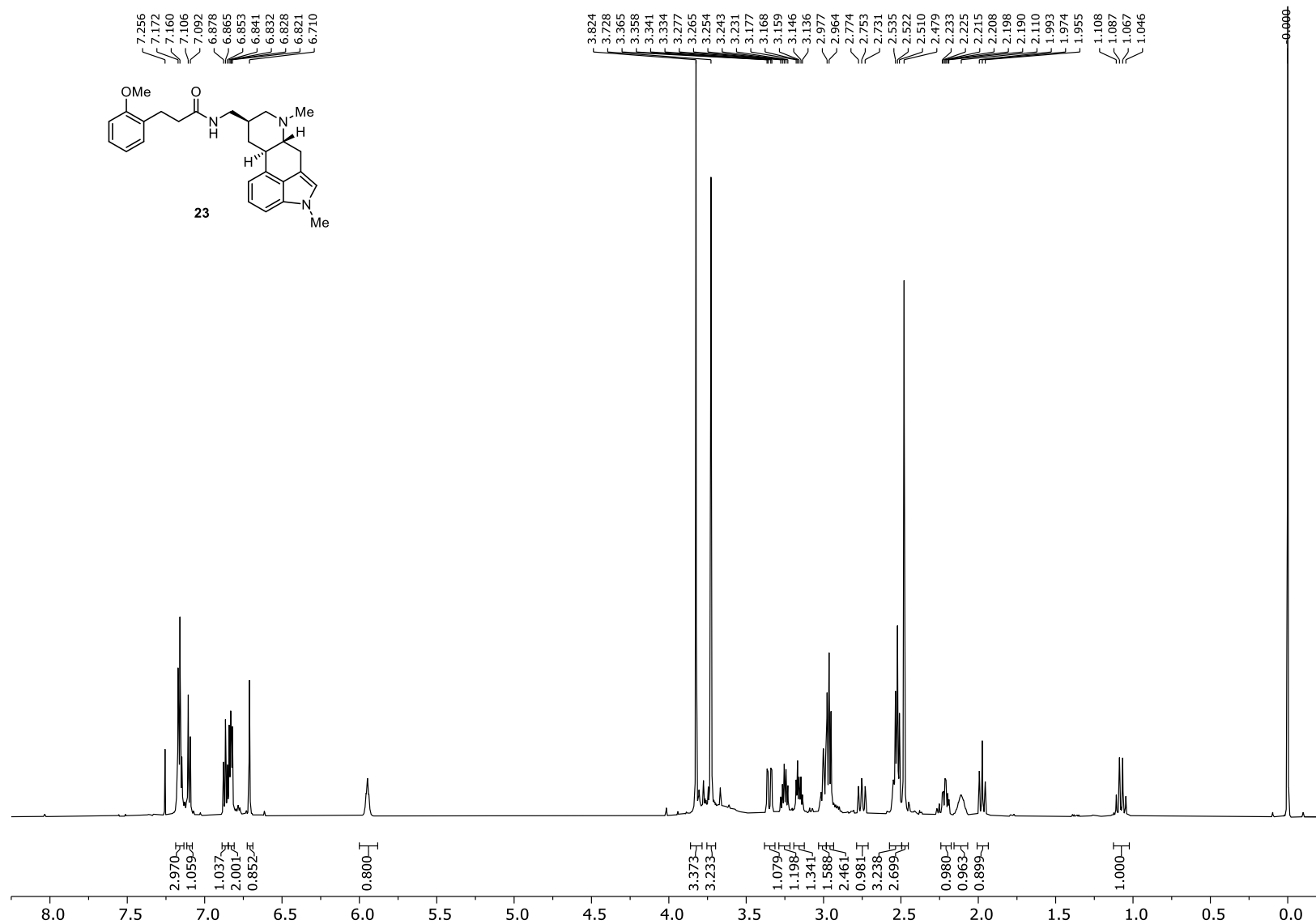
N-(4-Bromo-hydrocinnamoyl) ergoline derivative (**22**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



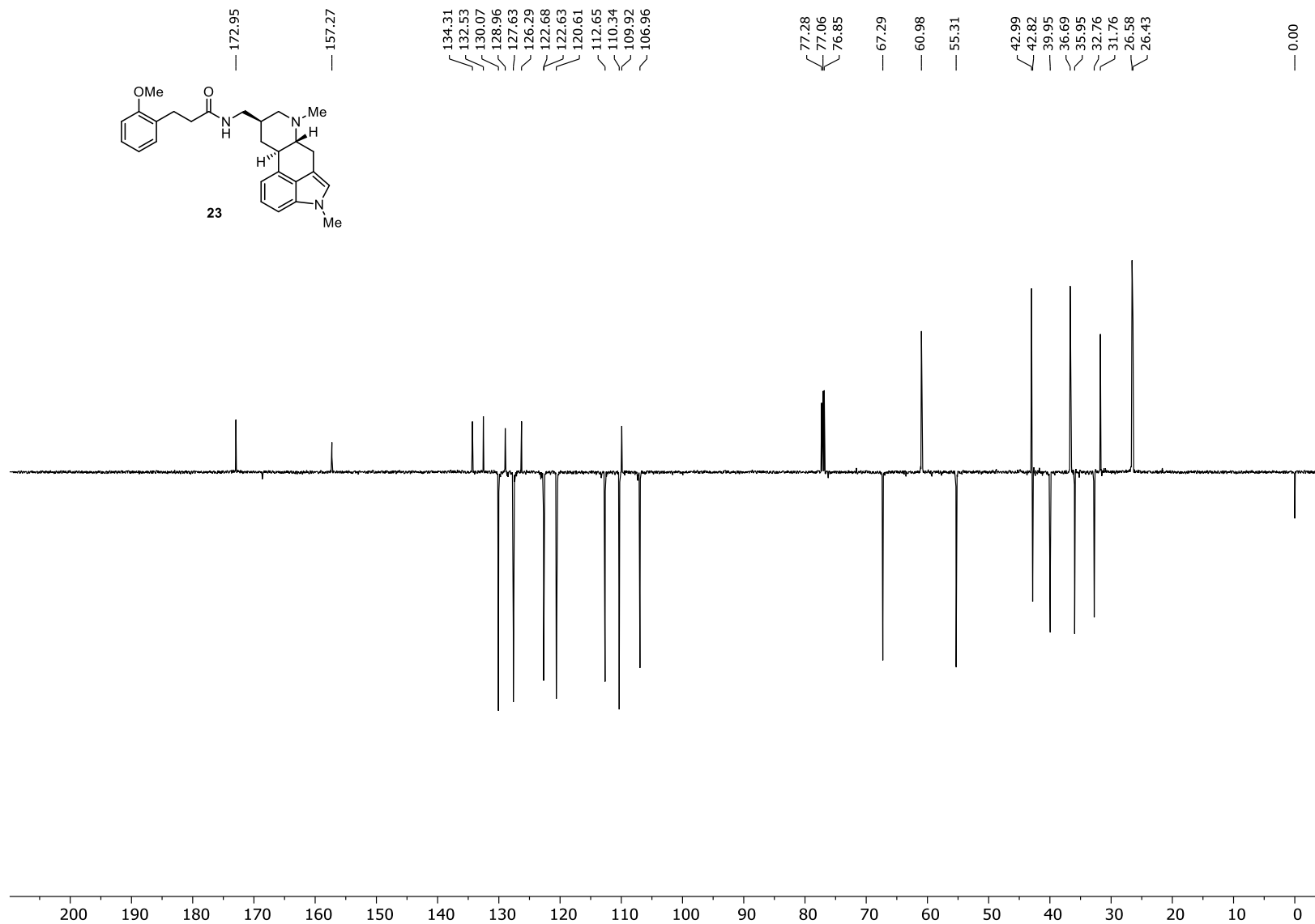
N-(4-Bromo-hydrocinnamoyl) ergoline derivative (**22**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



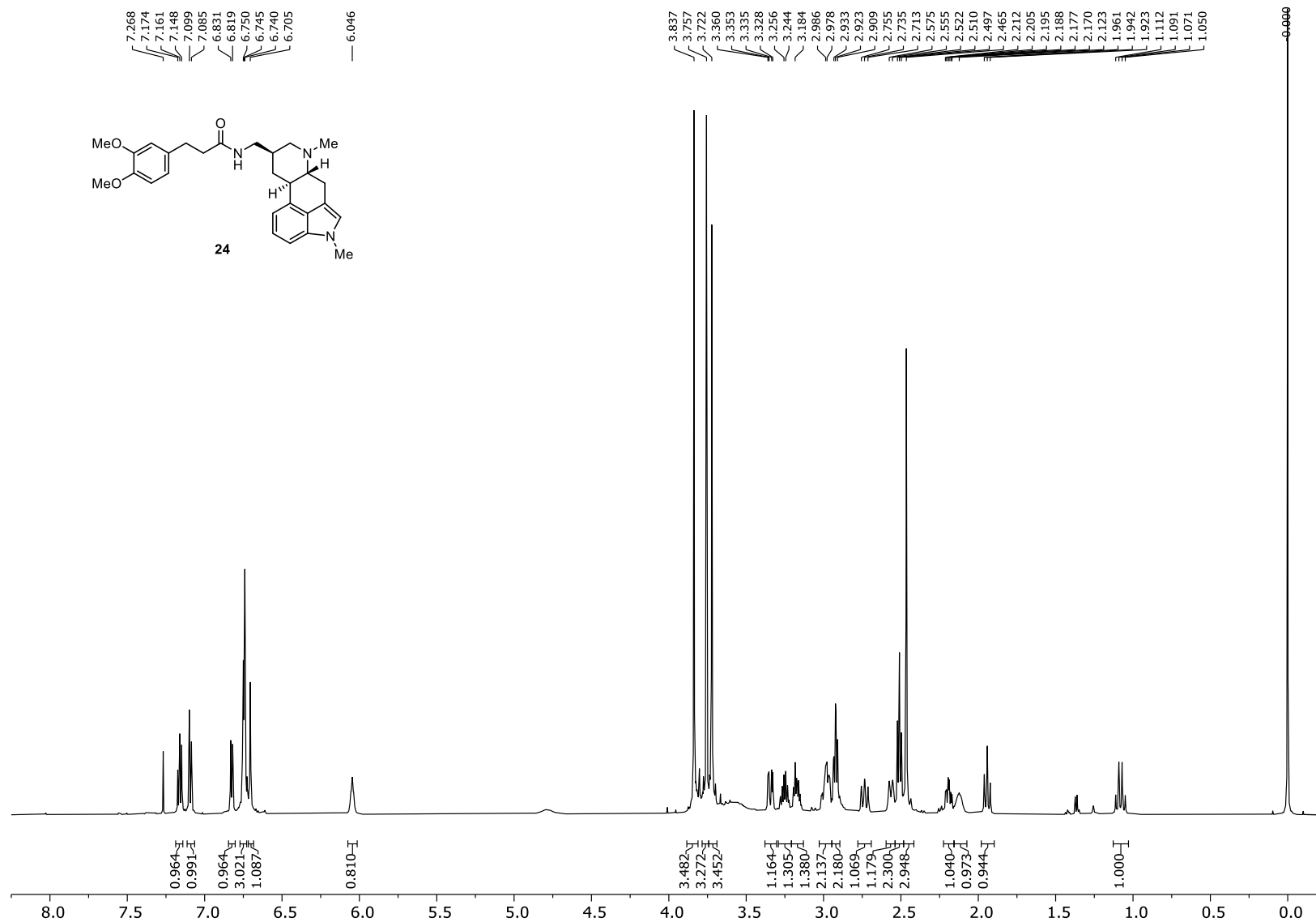
N-(2-Methoxy-hydrocinnamoyl) ergoline derivative (**23**) (^1H NMR; 600 MHz; CDCl_3 + TMS)



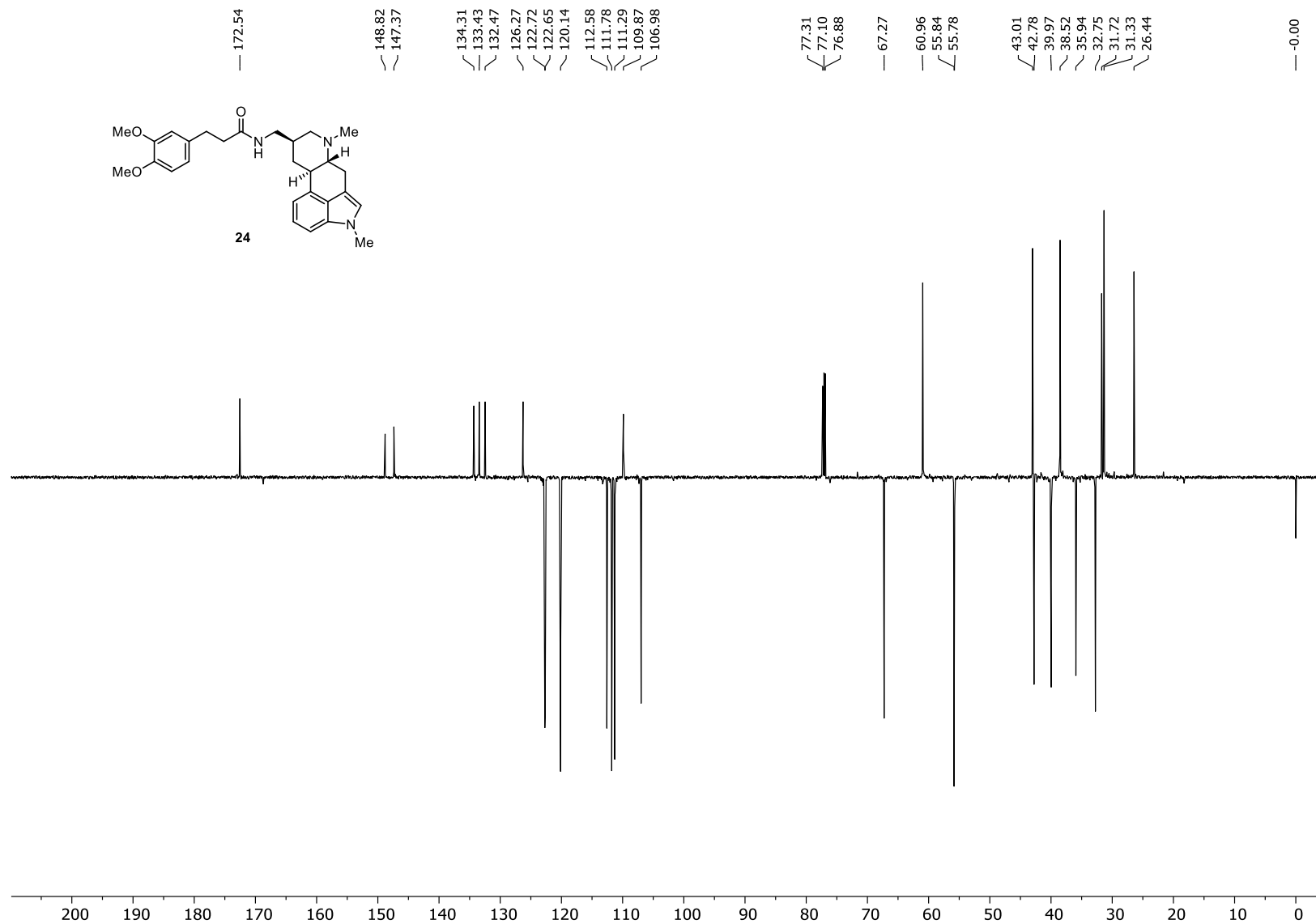
N-(2-Methoxy-hydrocinnamoyl) ergoline derivative (**23**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



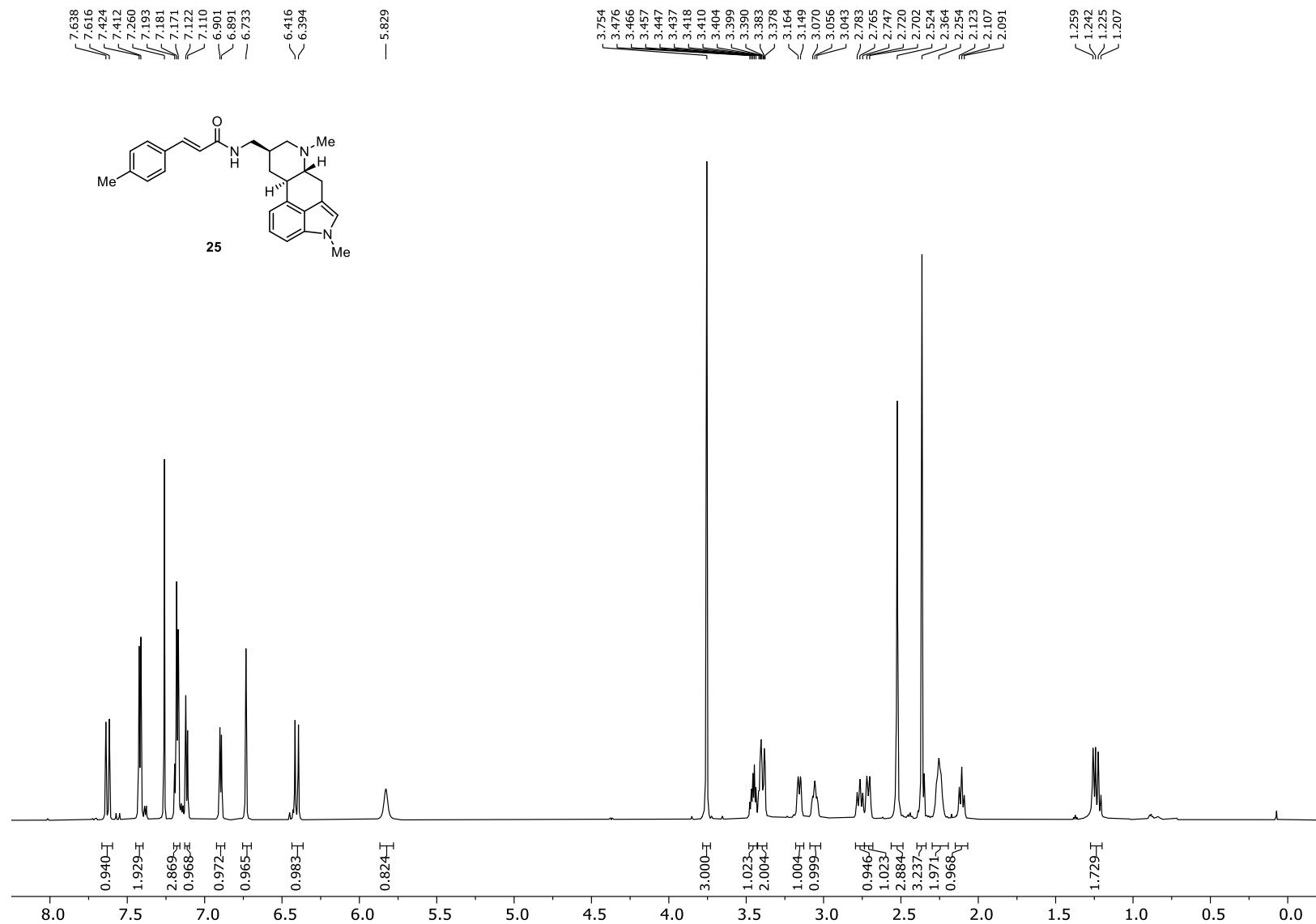
N-(3,4-Dimethoxy-hydrocinnamoyl) ergoline derivative (**24**) (¹H NMR; 600 MHz; CDCl₃ + TMS)



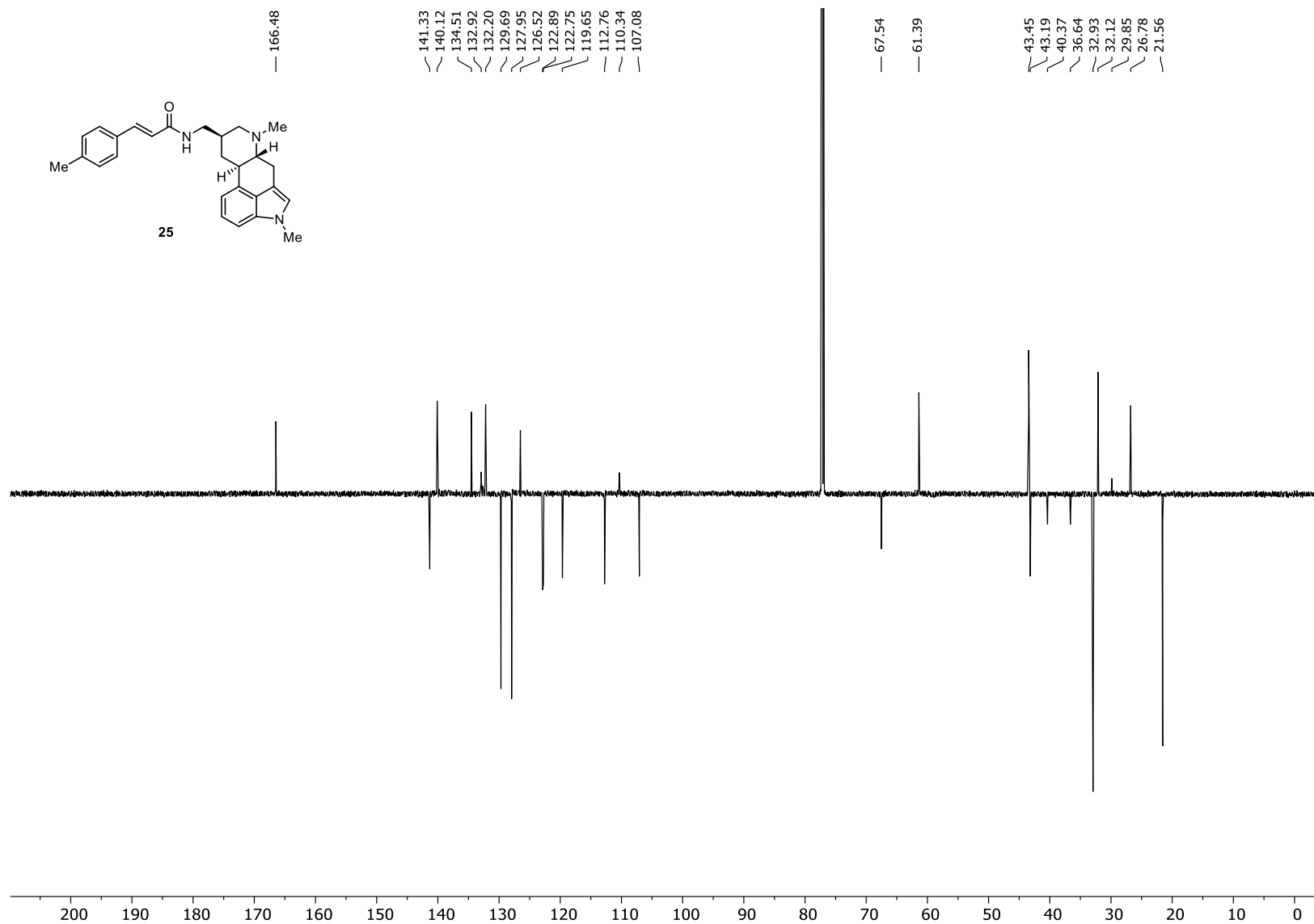
N-(3,4-Dimethoxy-hydrocinnamoyl) ergoline derivative (**24**) (^{13}C NMR; 150 MHz; CDCl_3 + TMS)



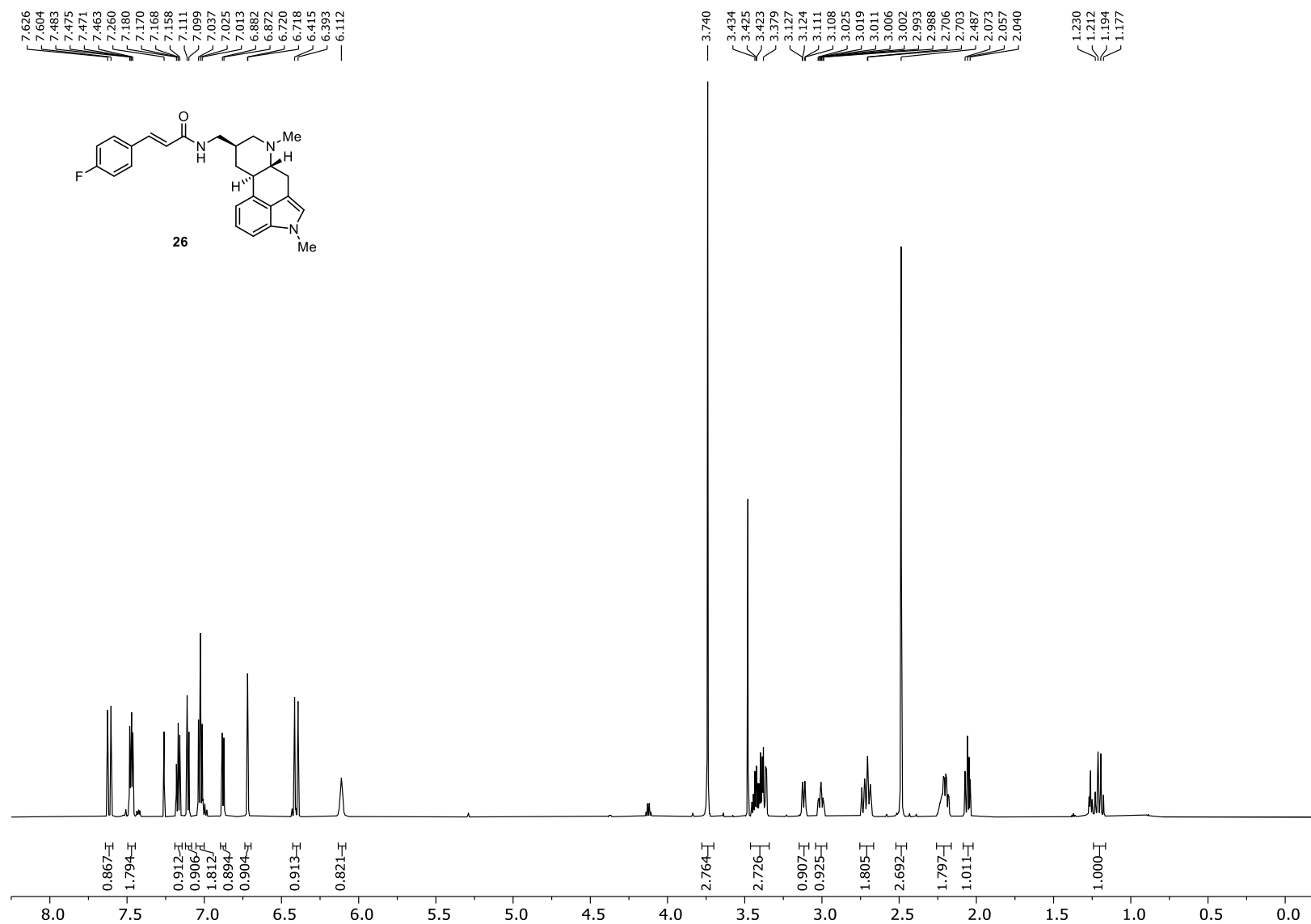
N-(4-Methyl-*trans*-cinnamoyl) ergoline derivative (**25**) (¹H NMR; 700 MHz; CDCl₃)



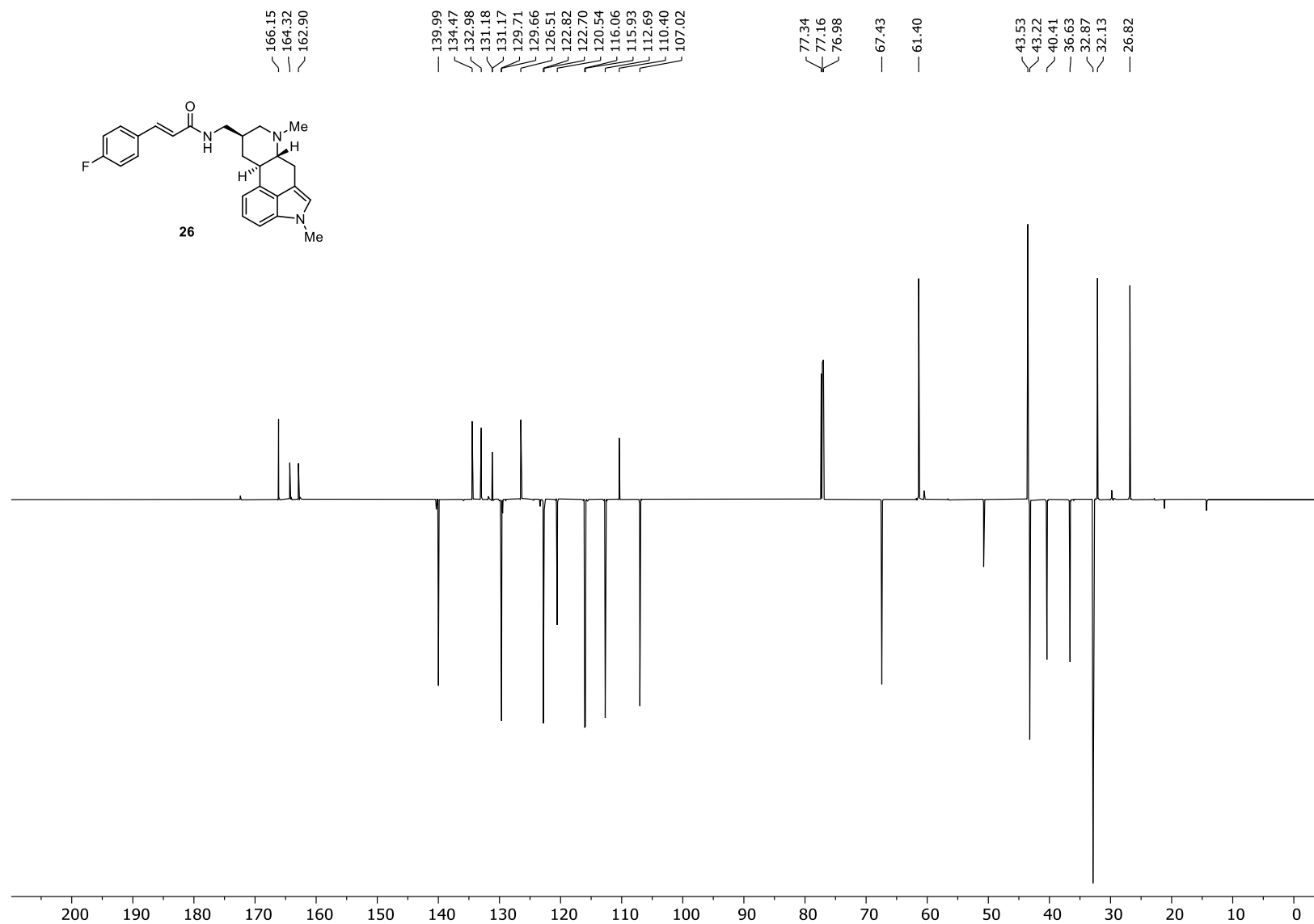
N-(4-Methyl-*trans*-cinnamoyl) ergoline derivative (**25**) (^{13}C NMR; 175 MHz; CDCl_3)



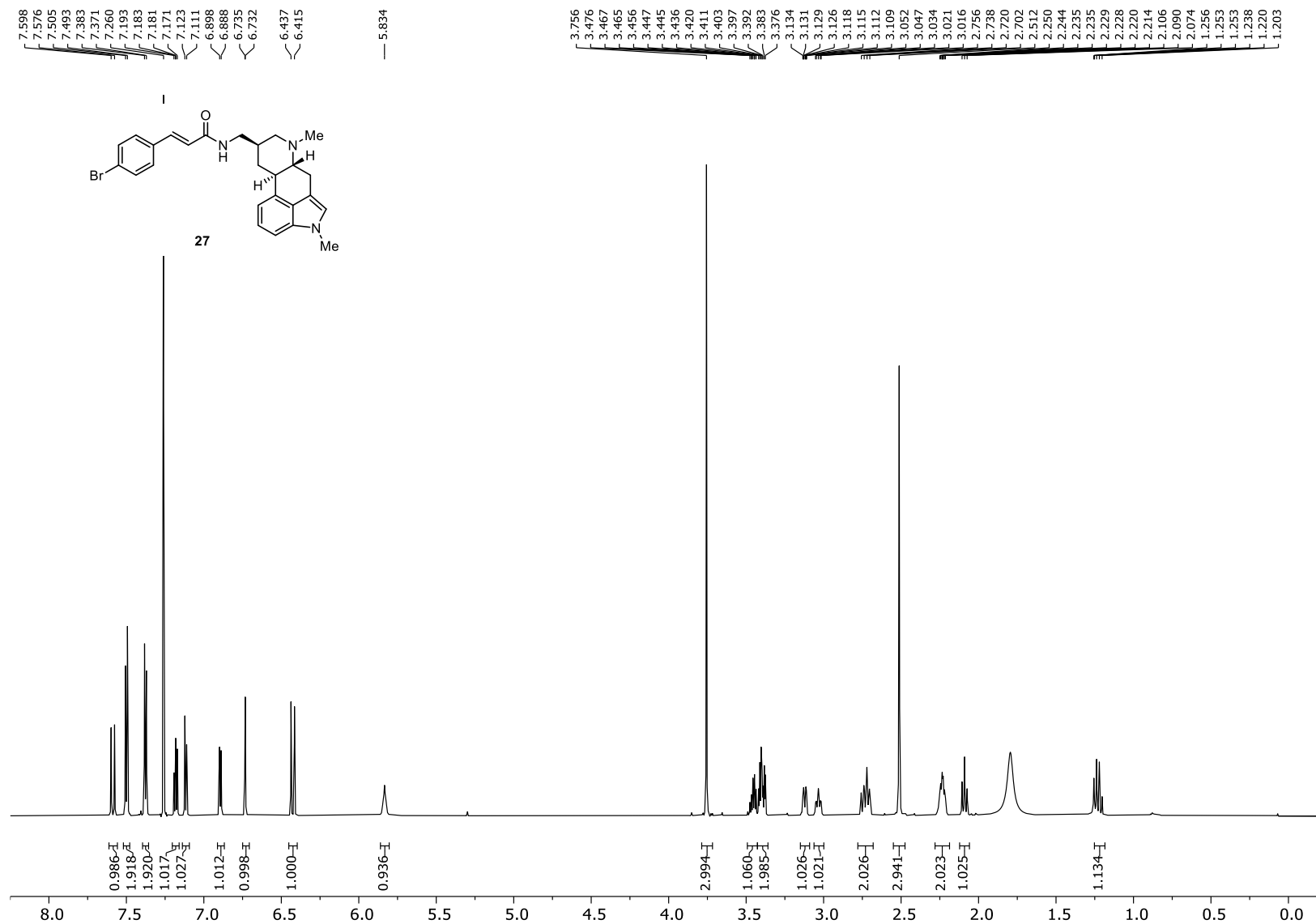
N-(4-Fluoro-*trans*-cinnamoyl) ergoline derivative (**26**) (^1H NMR; 700 MHz; CDCl_3)



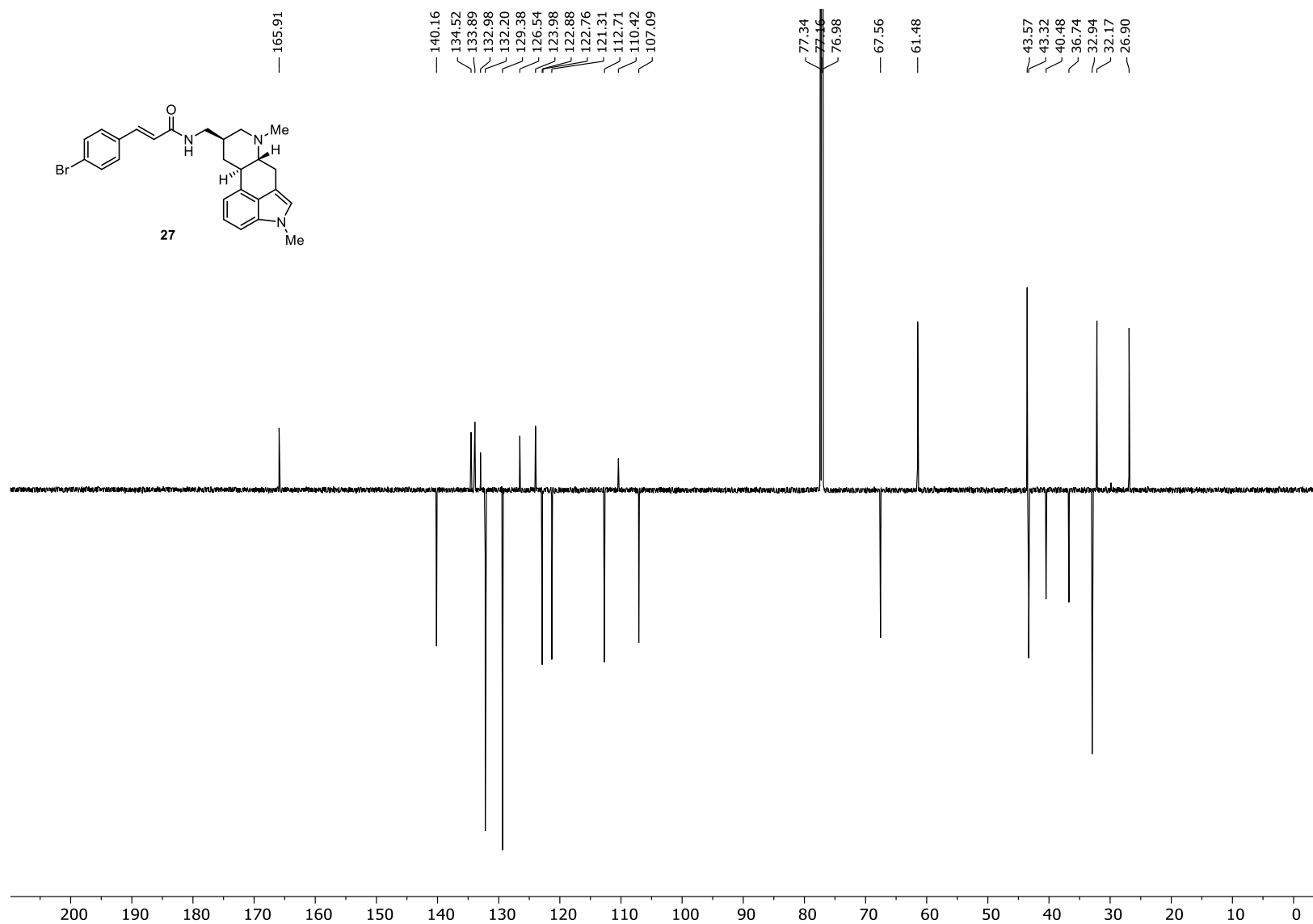
N-(4-Fluoro-*trans*-cinnamoyl) ergoline derivative (**26**) (^{13}C NMR; 175 MHz; CDCl_3)



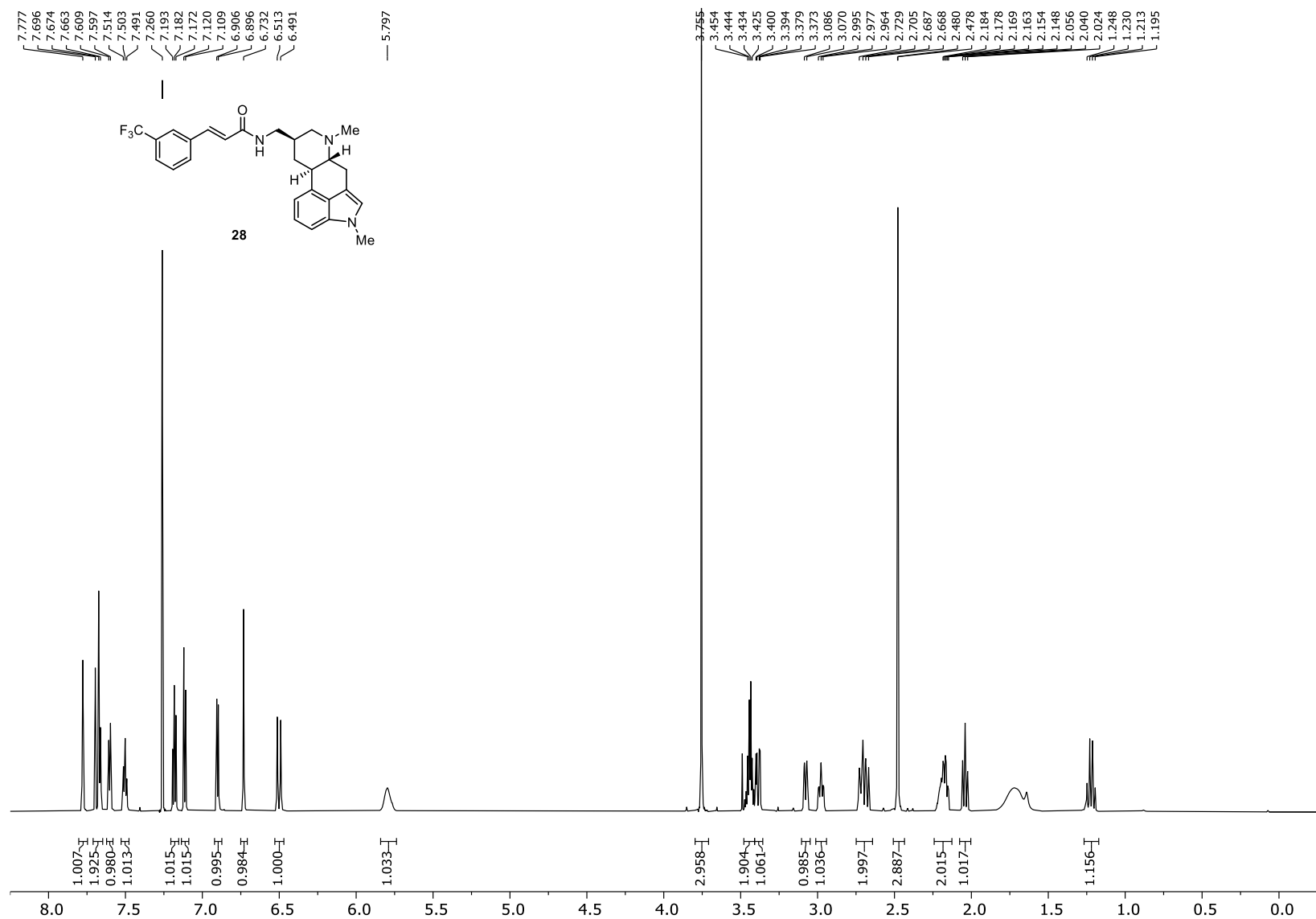
N-(4-Bromo-*trans*-cinnamoyl) ergoline derivative (**27**) (¹H NMR; 700 MHz; CDCl₃)



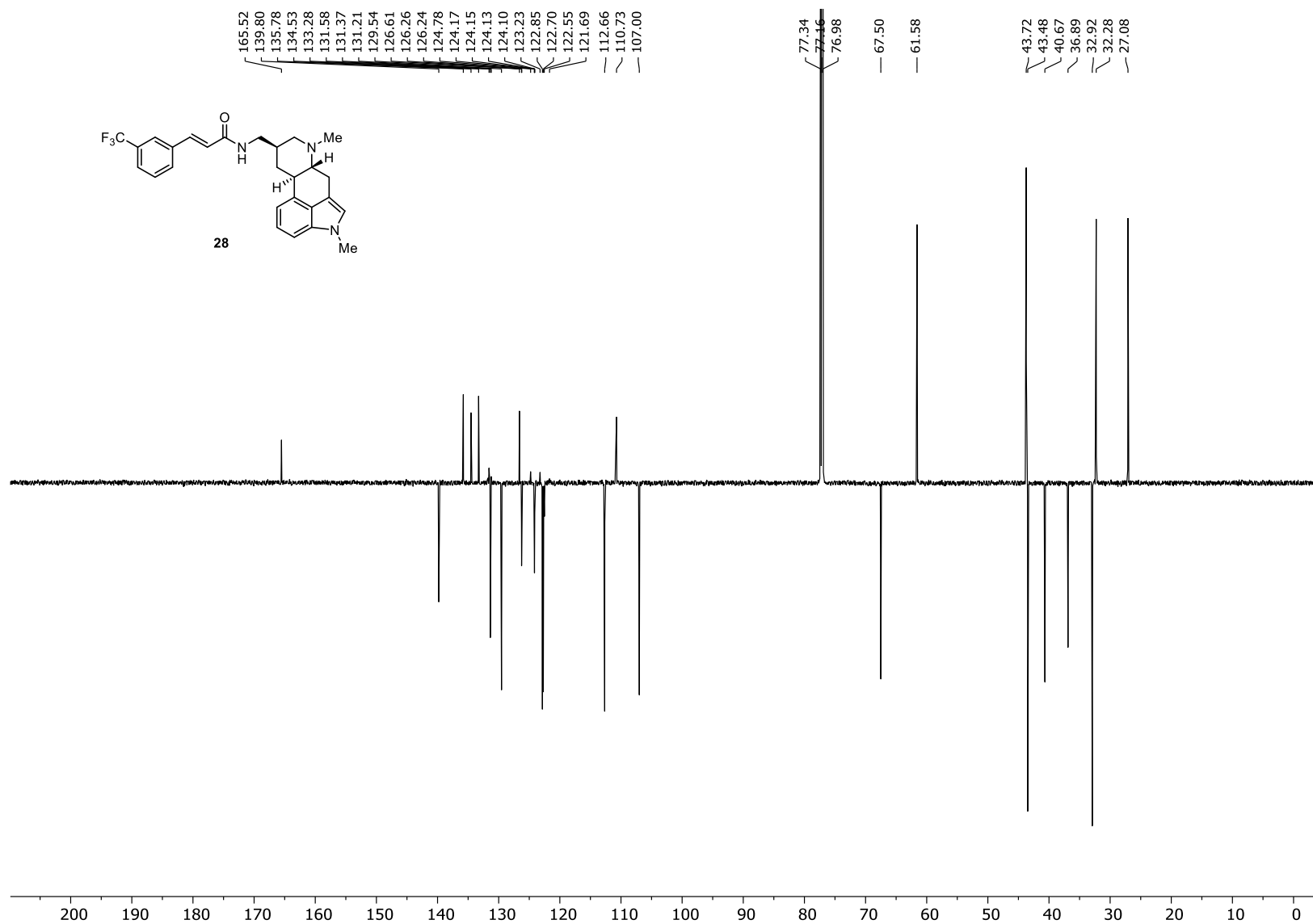
N-(4-Bromo-*trans*-cinnamoyl) ergoline derivative (**27**) (^{13}C NMR; 175 MHz; CDCl_3)



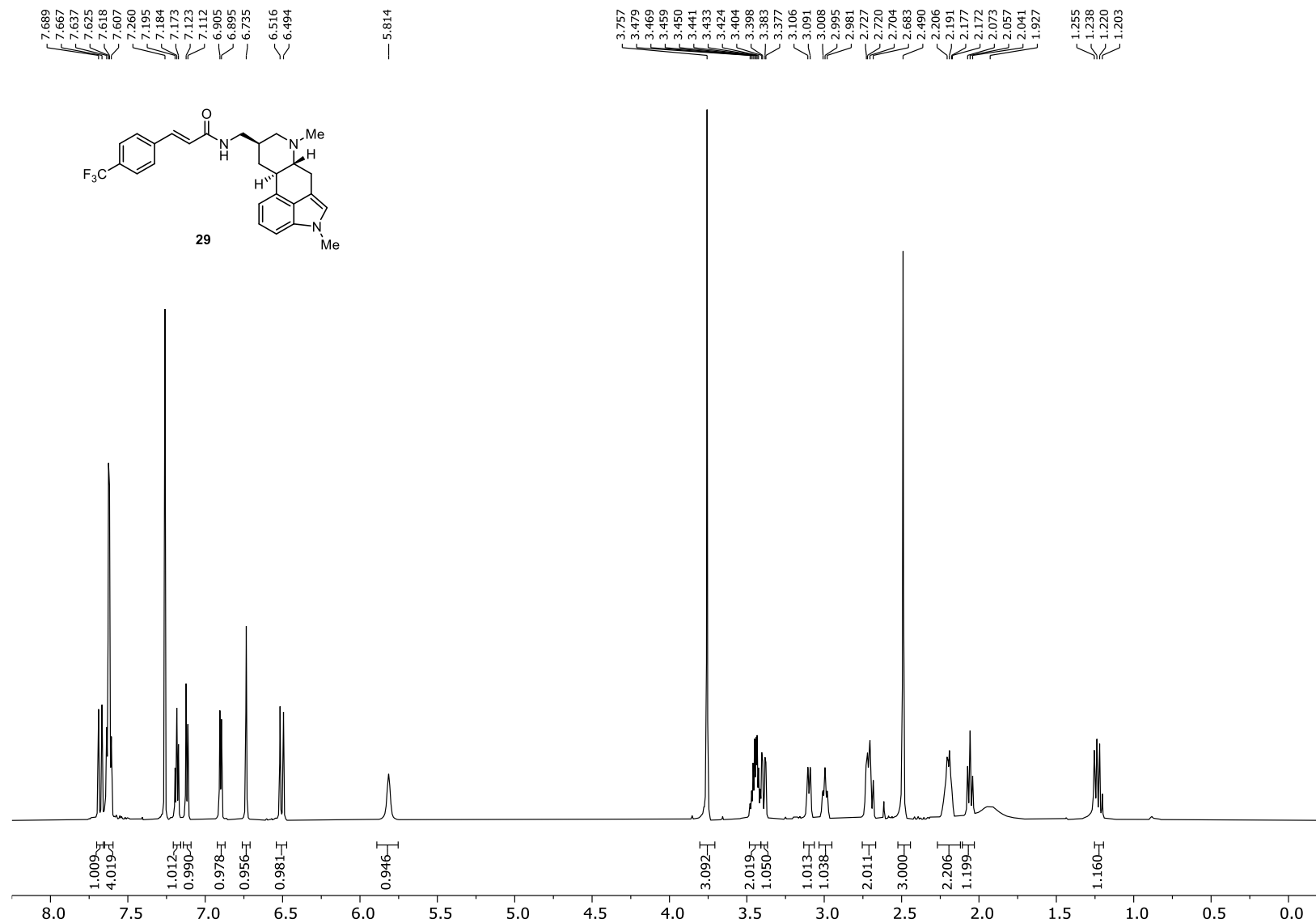
N-(3-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**28**) (^1H NMR; 700 MHz; CDCl_3)



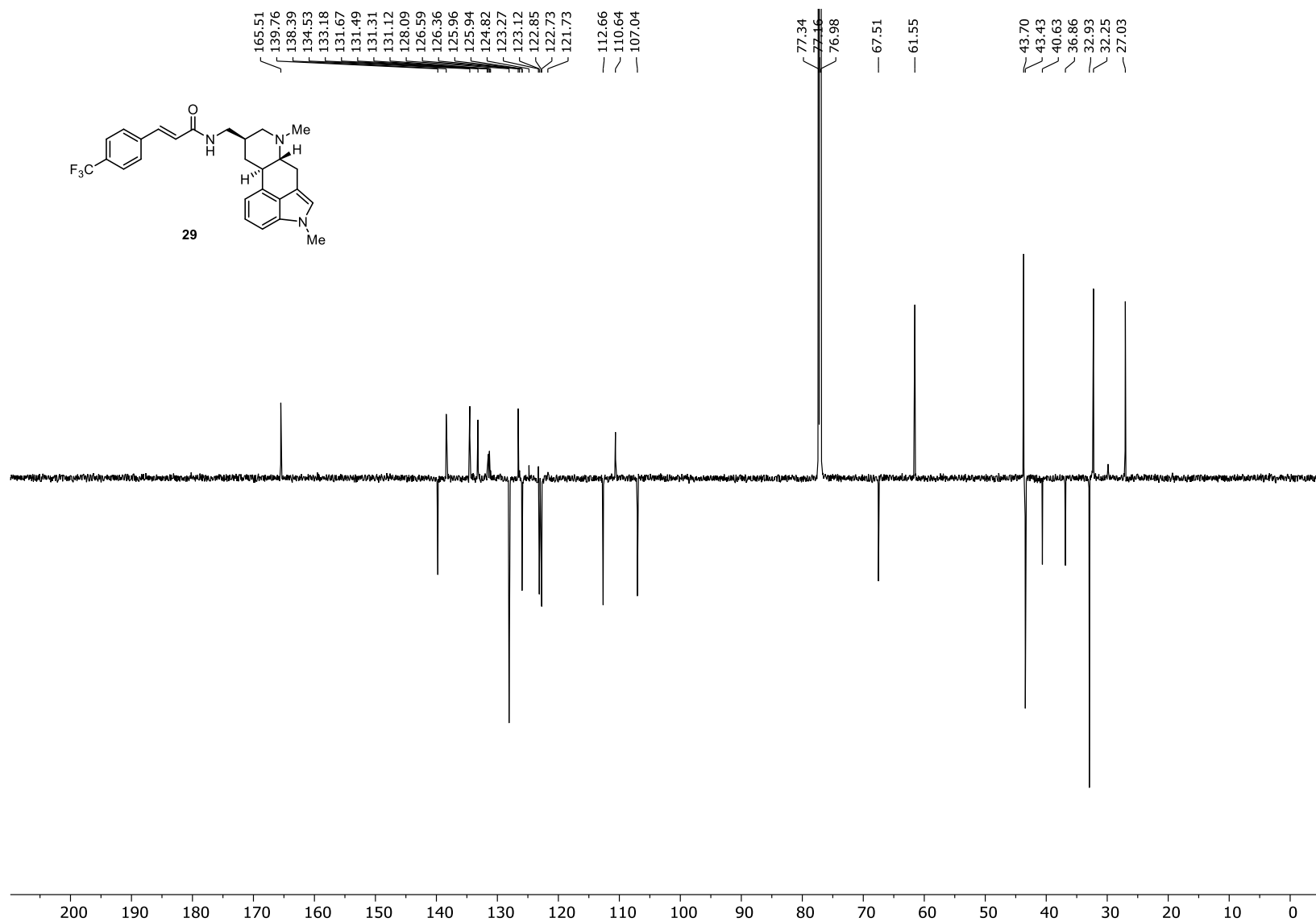
N-(3-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**28**) (^{13}C NMR; 175 MHz; CDCl_3)



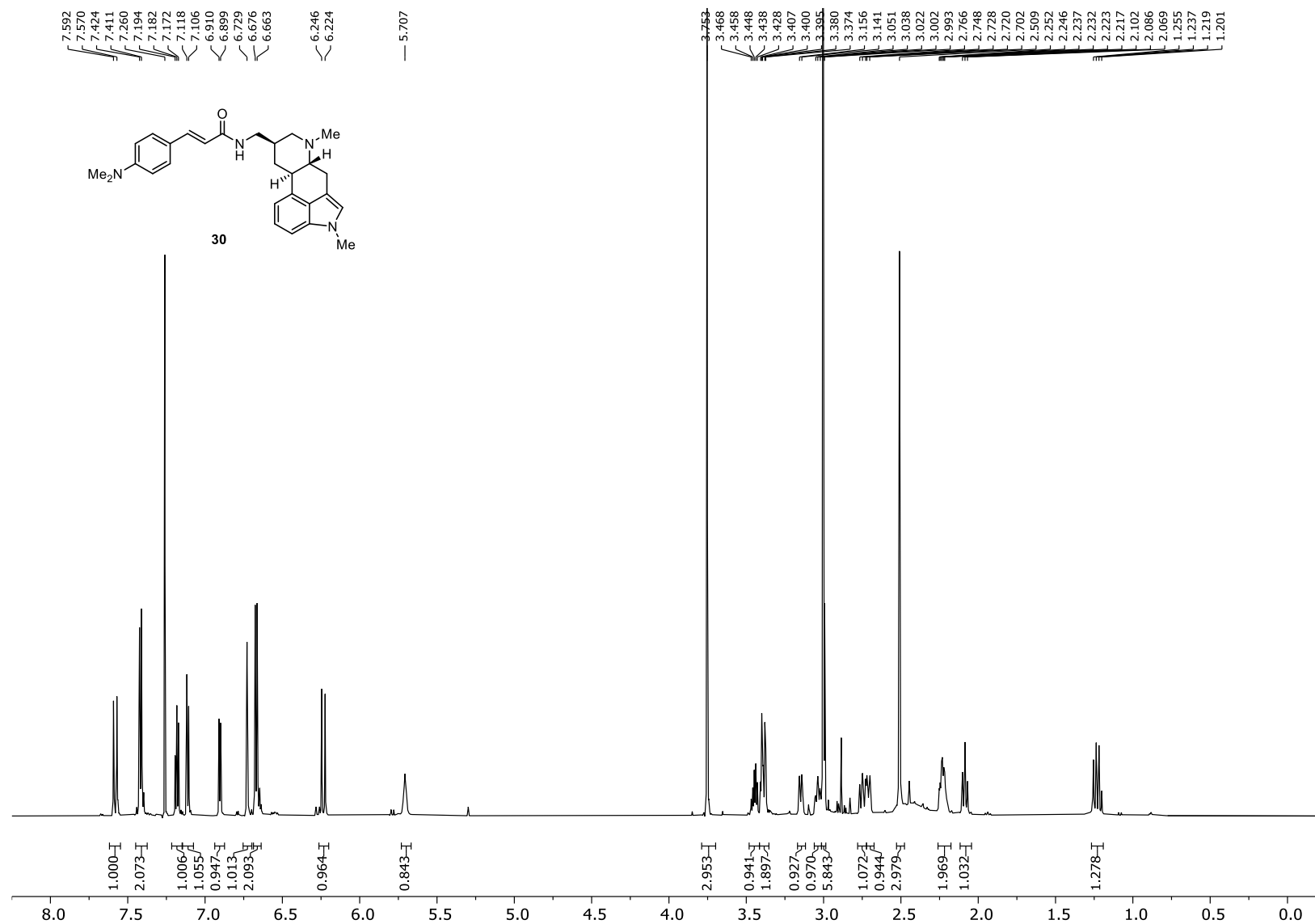
N-(4-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**29**) (^1H NMR; 700 MHz; CDCl_3)



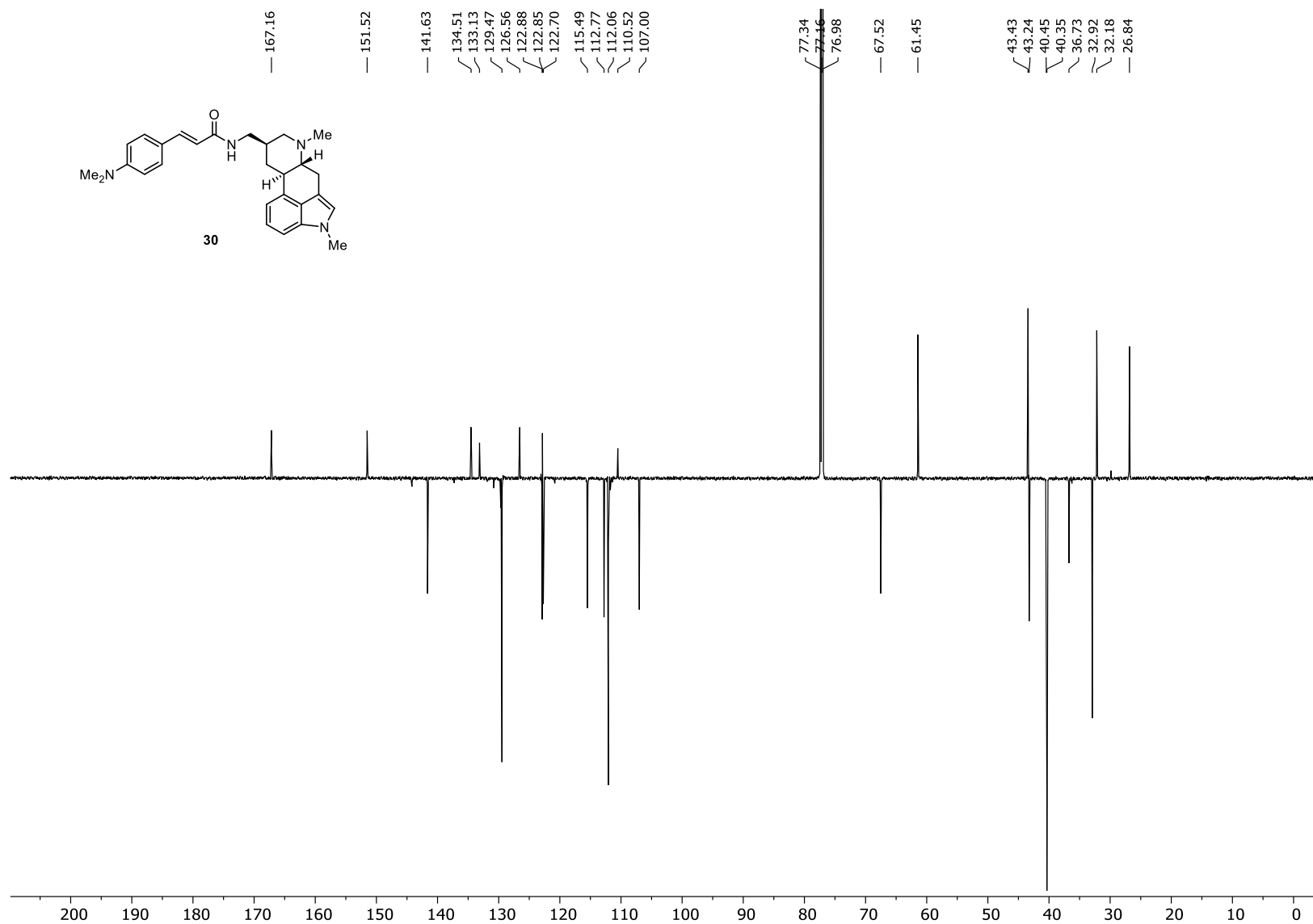
N-(4-Trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**29**) (^{13}C NMR; 175 MHz; CDCl_3)



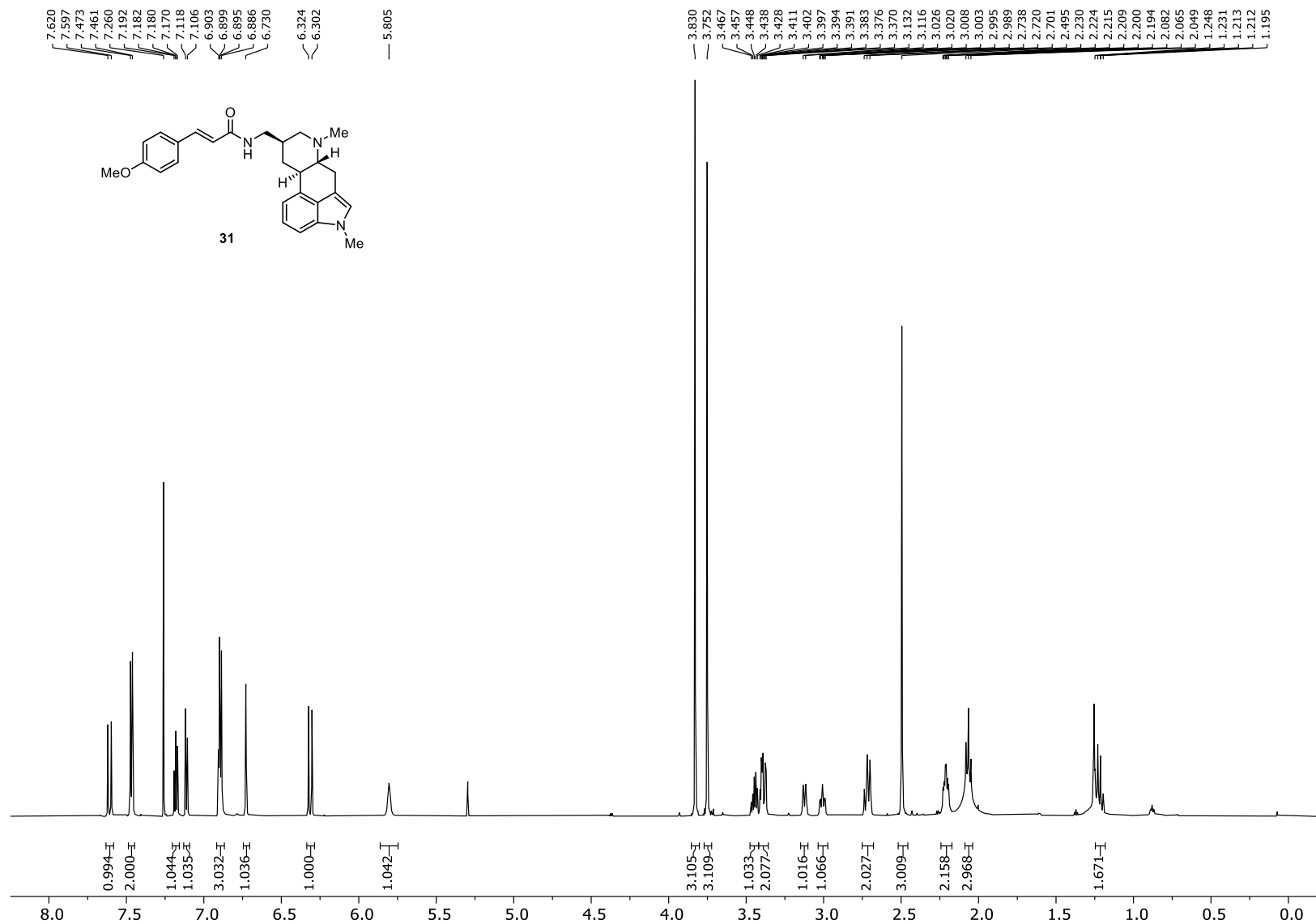
N-(4-Dimethylamino-*trans*-cinnamoyl) ergoline derivative (**30**) (^1H NMR; 700 MHz; CDCl_3)



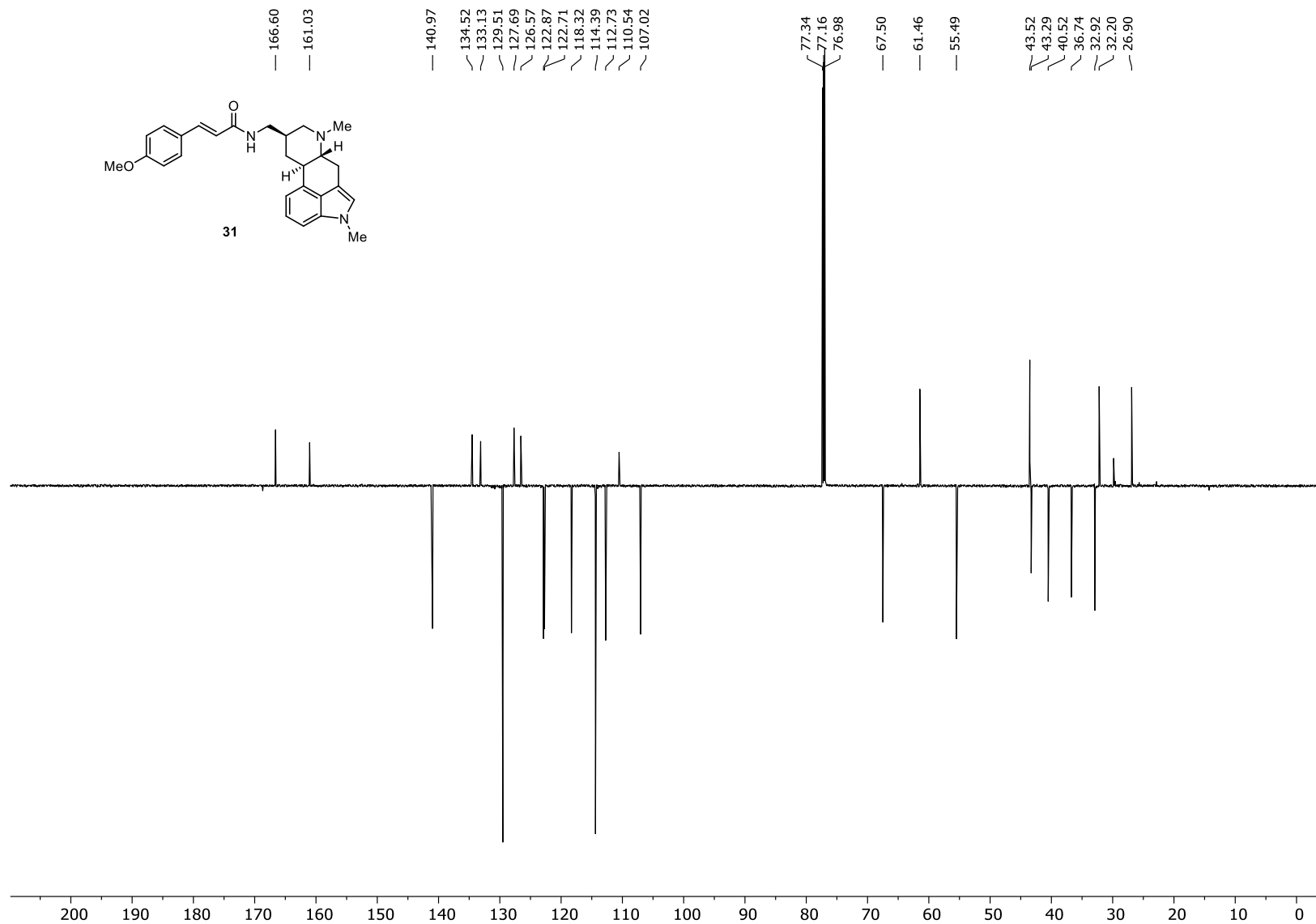
N-(4-Dimethylamino-*trans*-cinnamoyl) ergoline derivative (**30**) (^{13}C NMR; 175 MHz; CDCl_3)



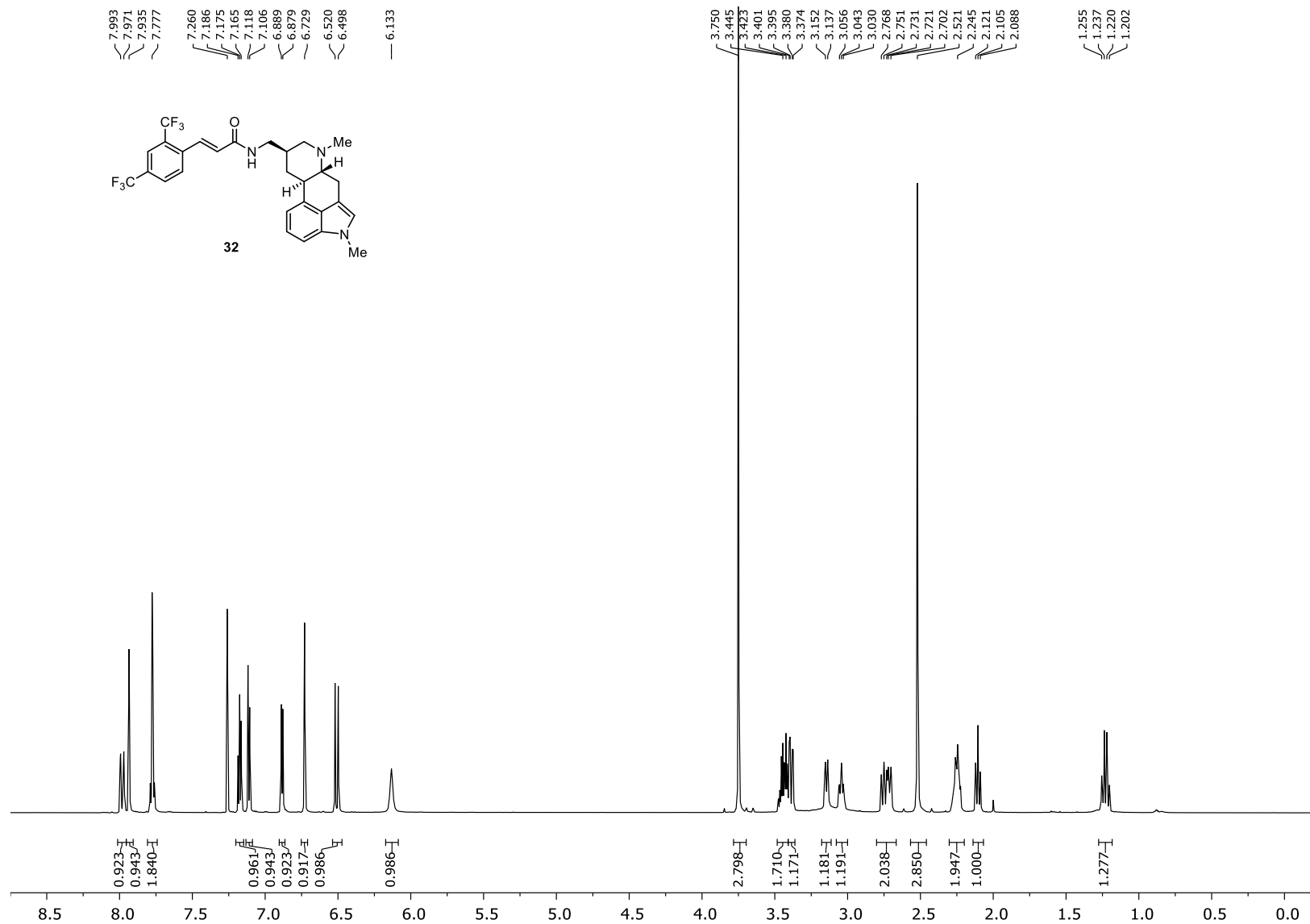
N-(4-Methoxy-*trans*-cinnamoyl) ergoline derivative (**31**) (^1H NMR; 700 MHz; CDCl_3)



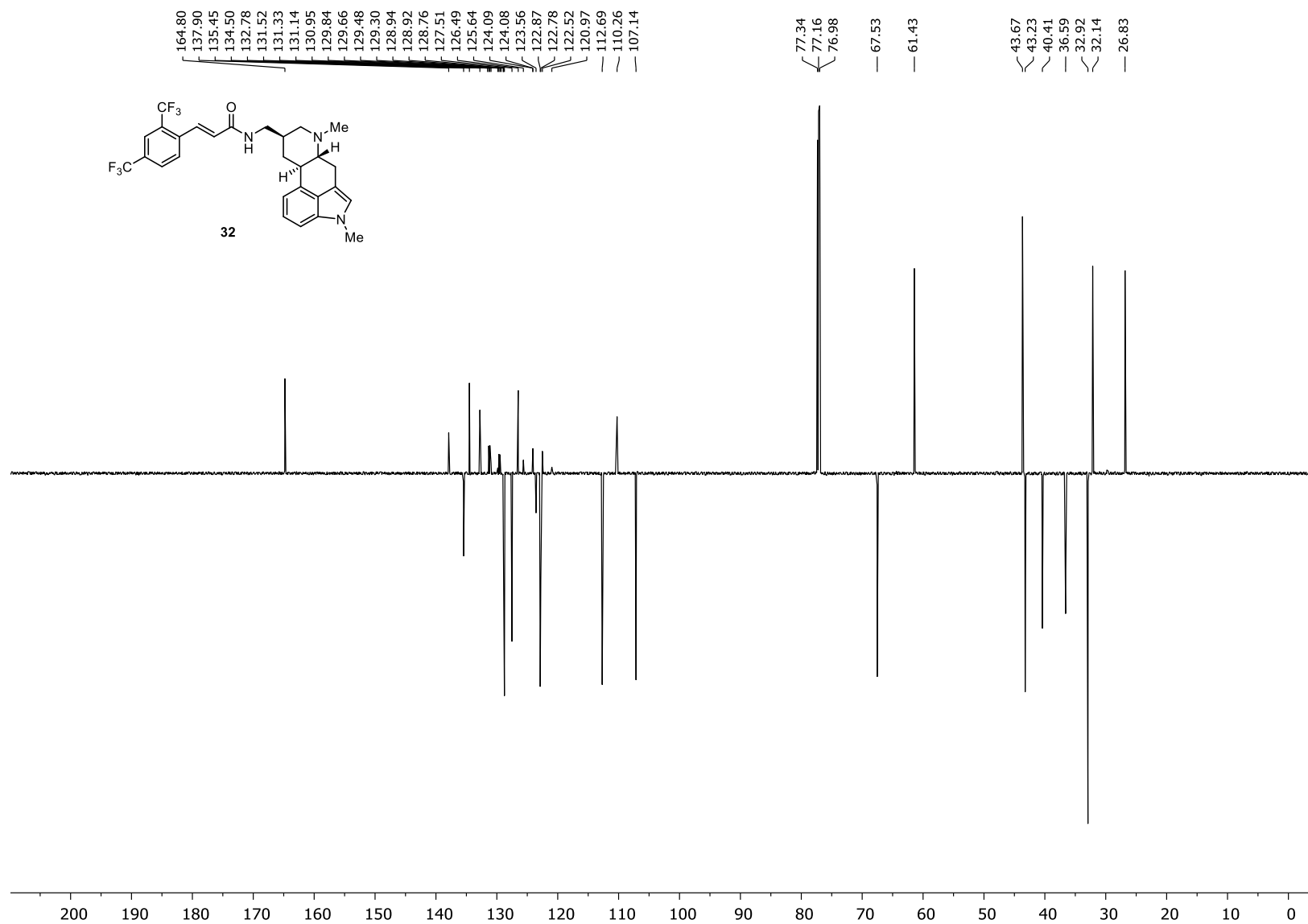
N-(4-Methoxy-*trans*-cinnamoyl) ergoline derivative (**31**) (^{13}C NMR; 175 MHz; CDCl_3)



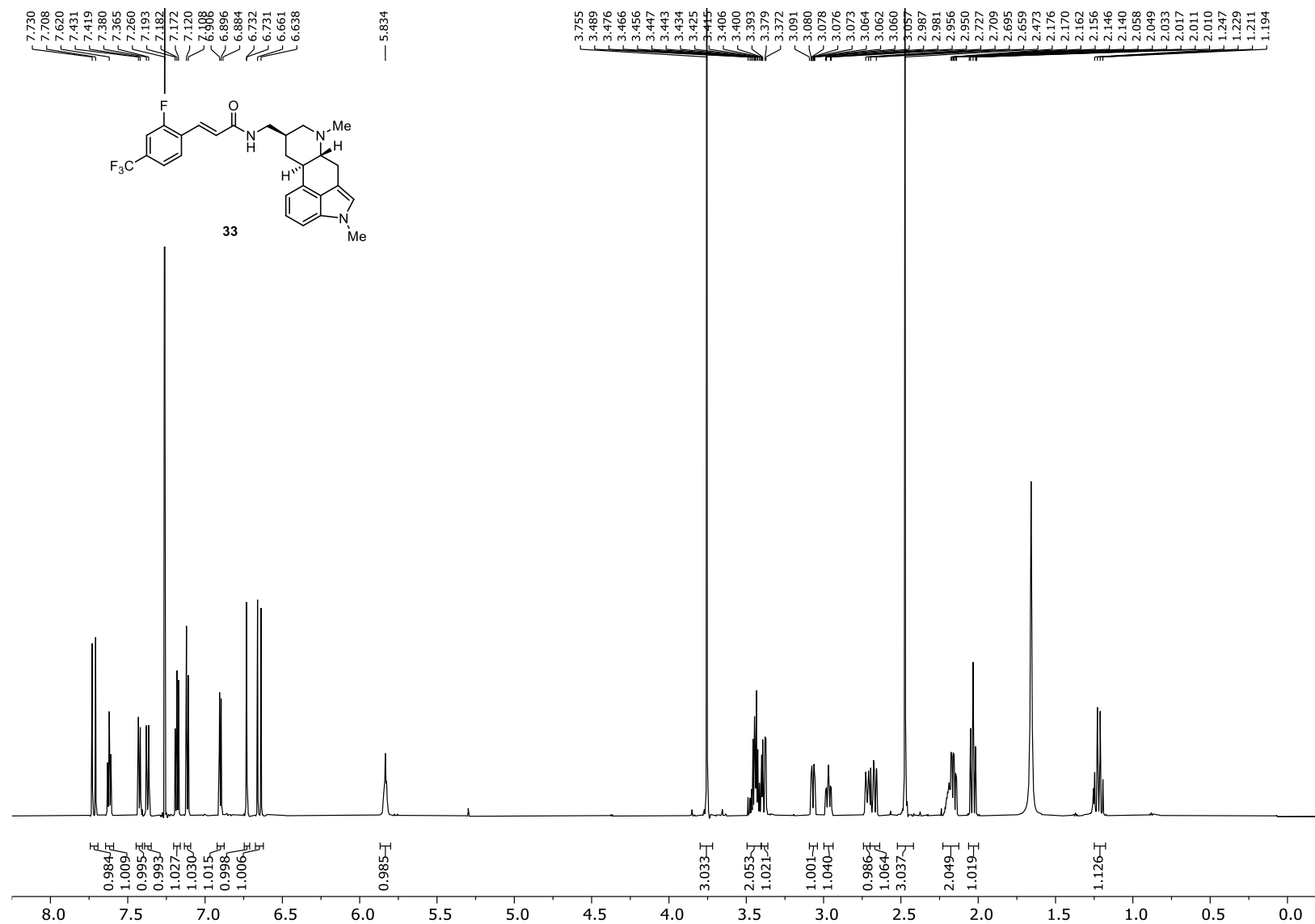
N-(2,4-Bis-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**32**) (^1H NMR; 700 MHz; CDCl_3)



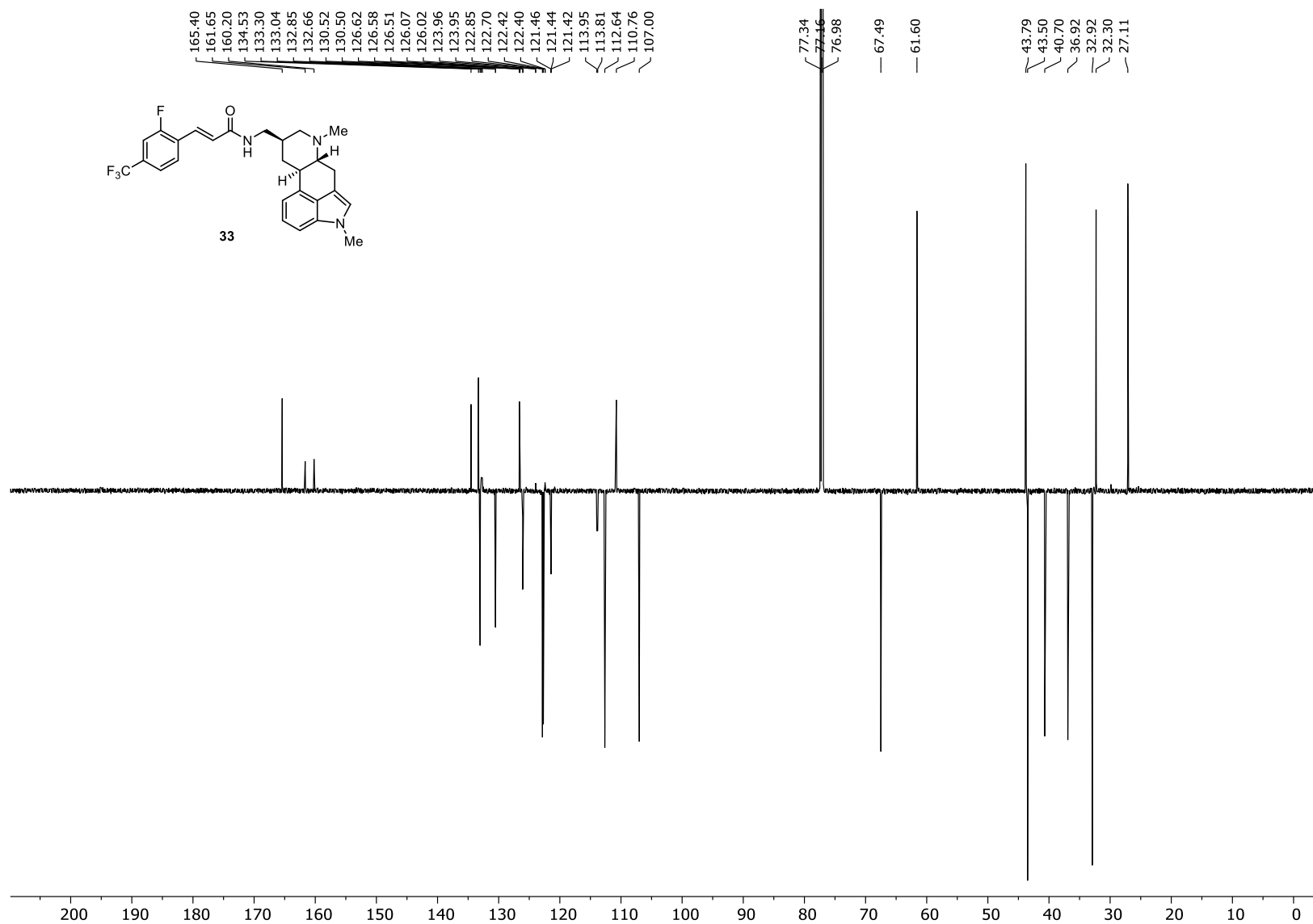
N-(2,4-Bis-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**32**) (^{13}C NMR; 175 MHz; CDCl_3)



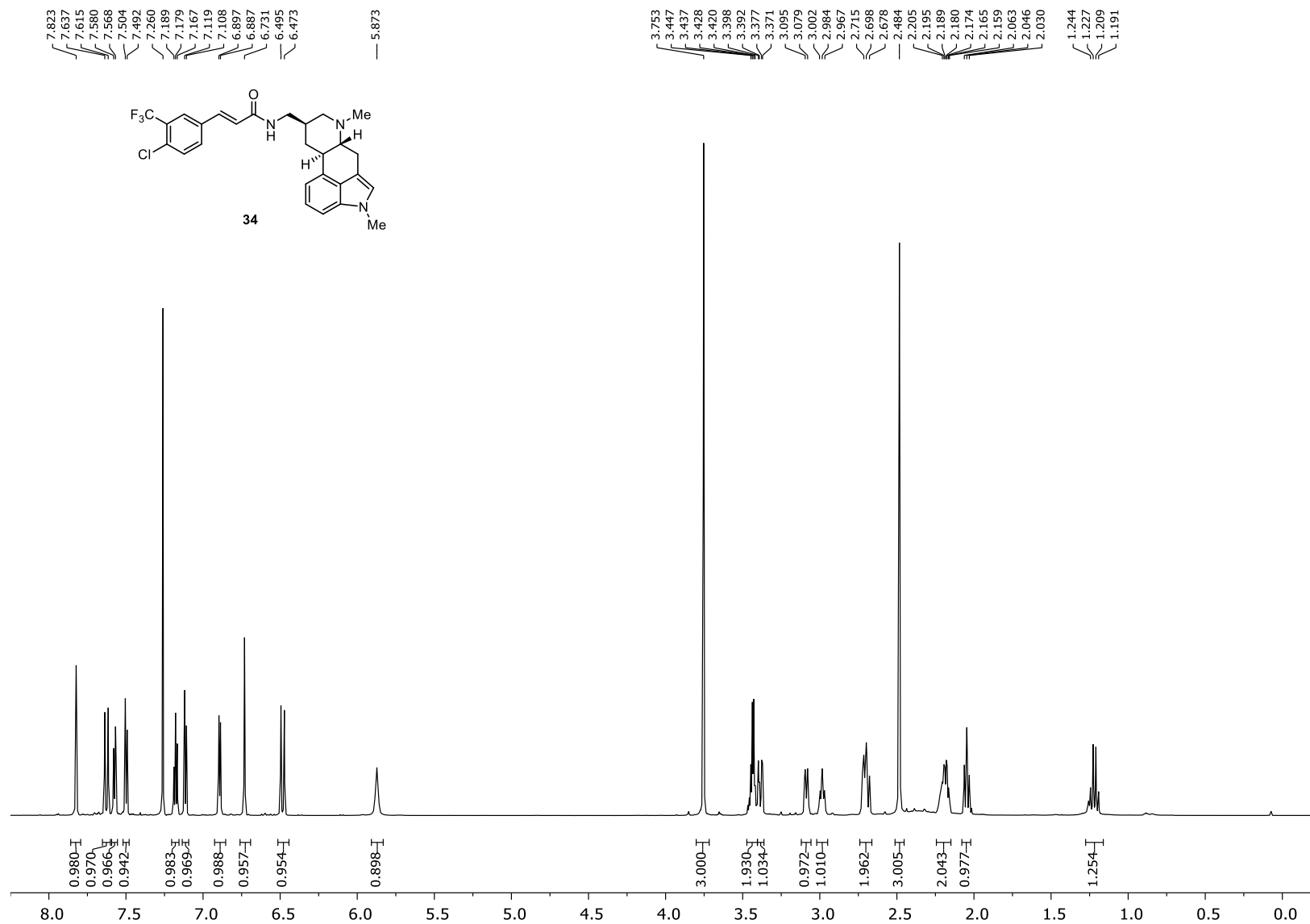
N-(2-Fluoro-4-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**33**) (^1H NMR; 700 MHz; CDCl_3)



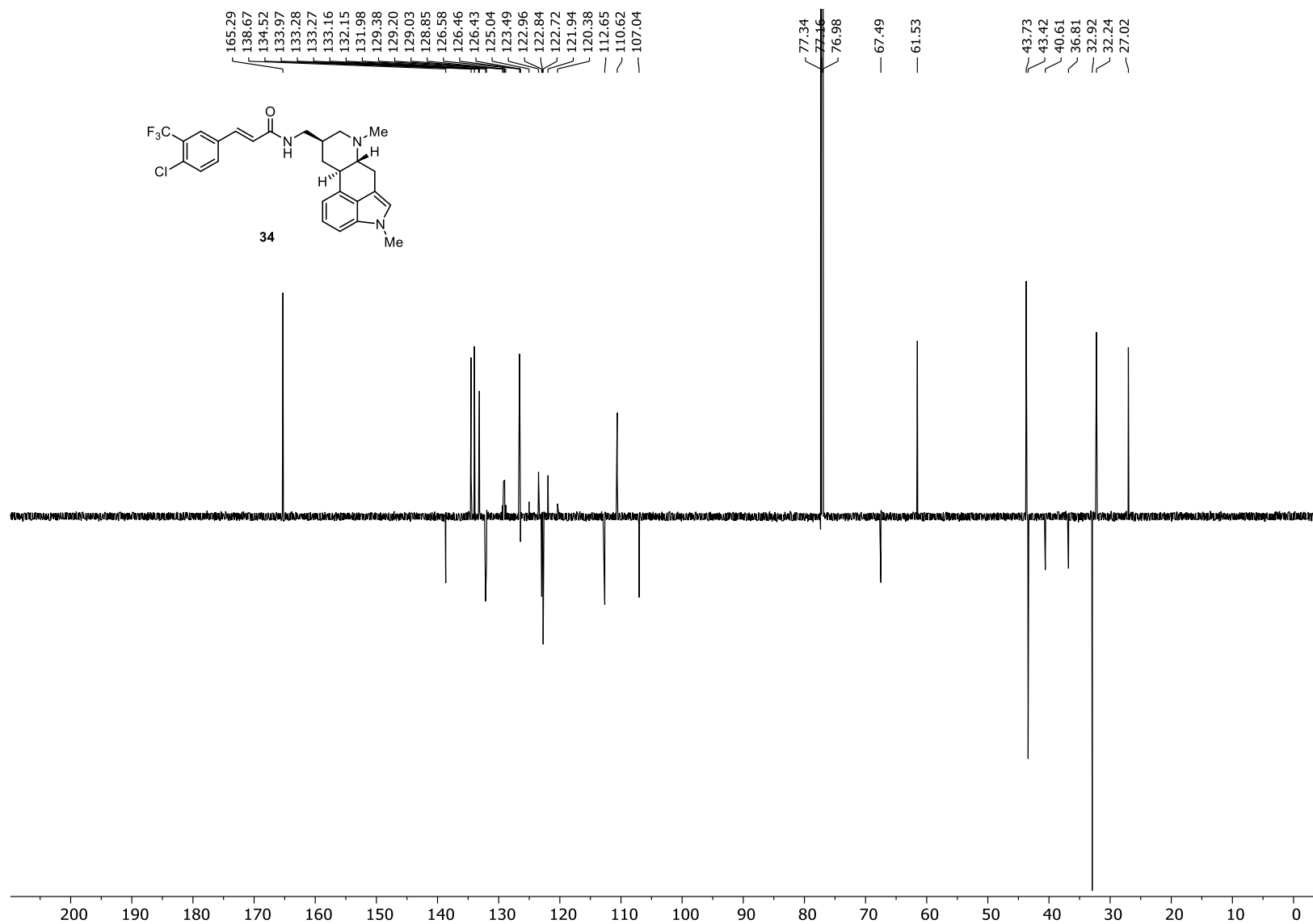
N-(2-Fluoro-4-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**33**) (^{13}C NMR; 175 MHz; CDCl_3)



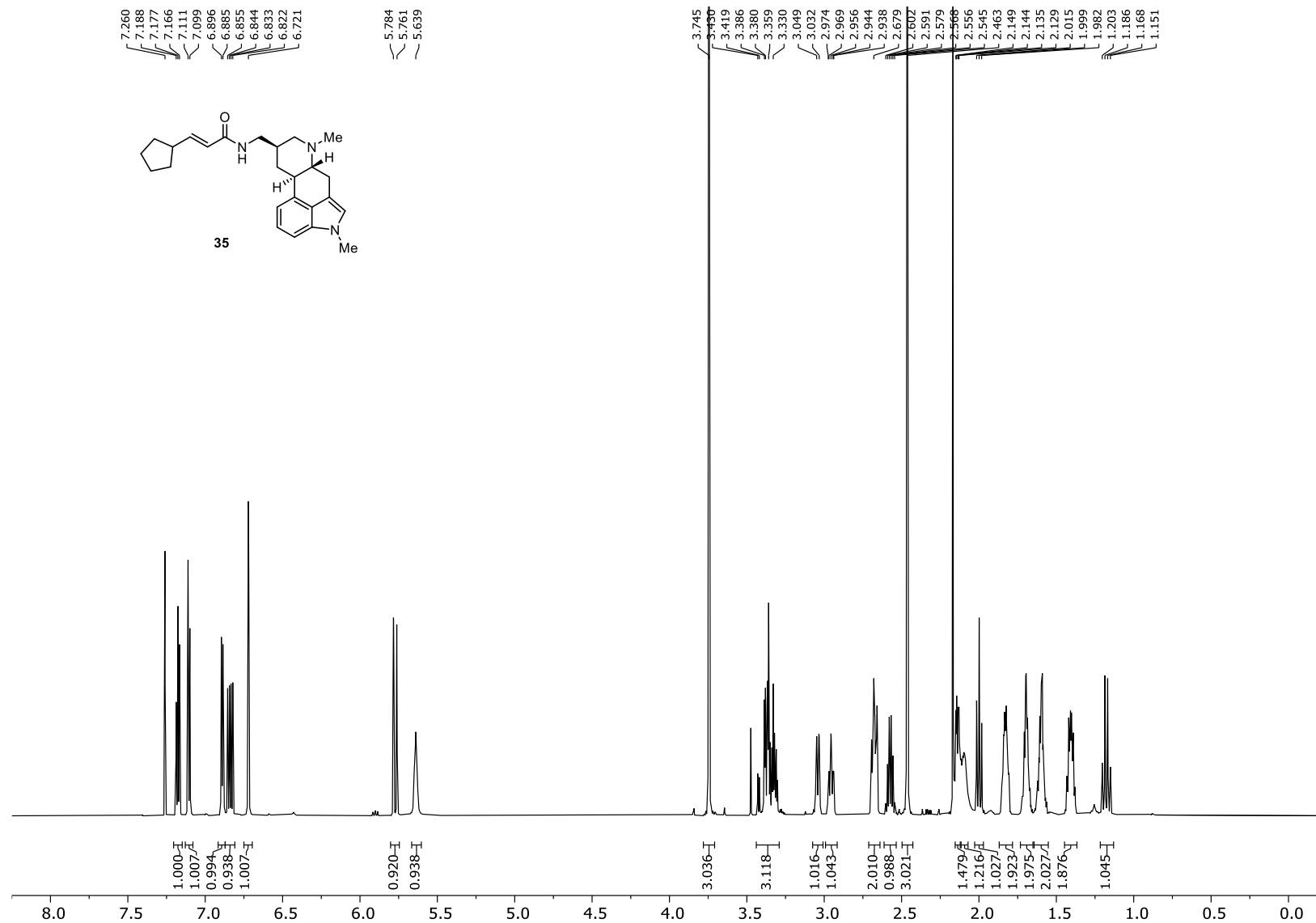
N-(4-Chloro-3-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**34**) (^1H NMR; 700 MHz; CDCl_3)



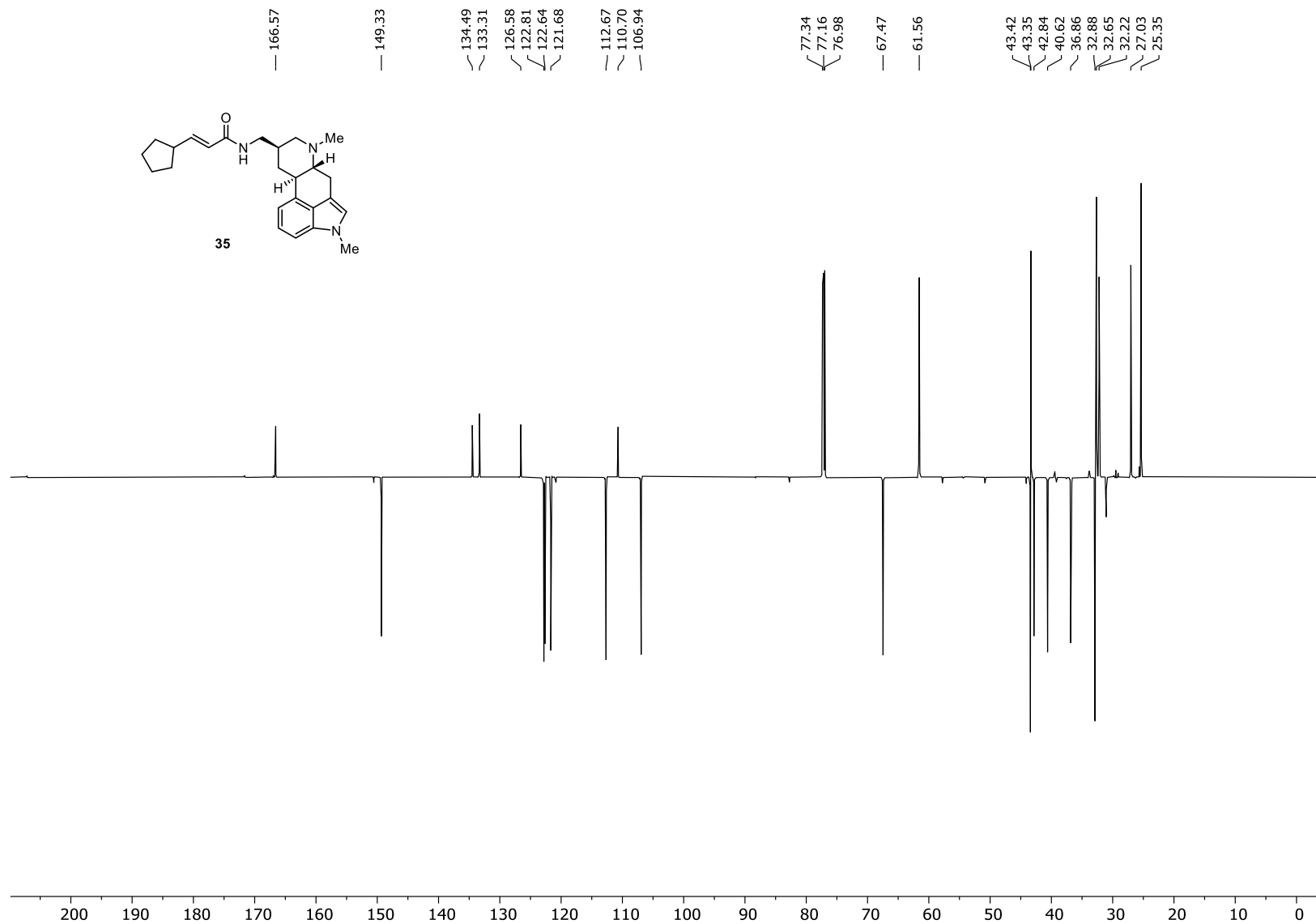
N-(4-Chloro-3-trifluoromethyl-*trans*-cinnamoyl) ergoline derivative (**34**) (^{13}C NMR; 175 MHz; CDCl_3)



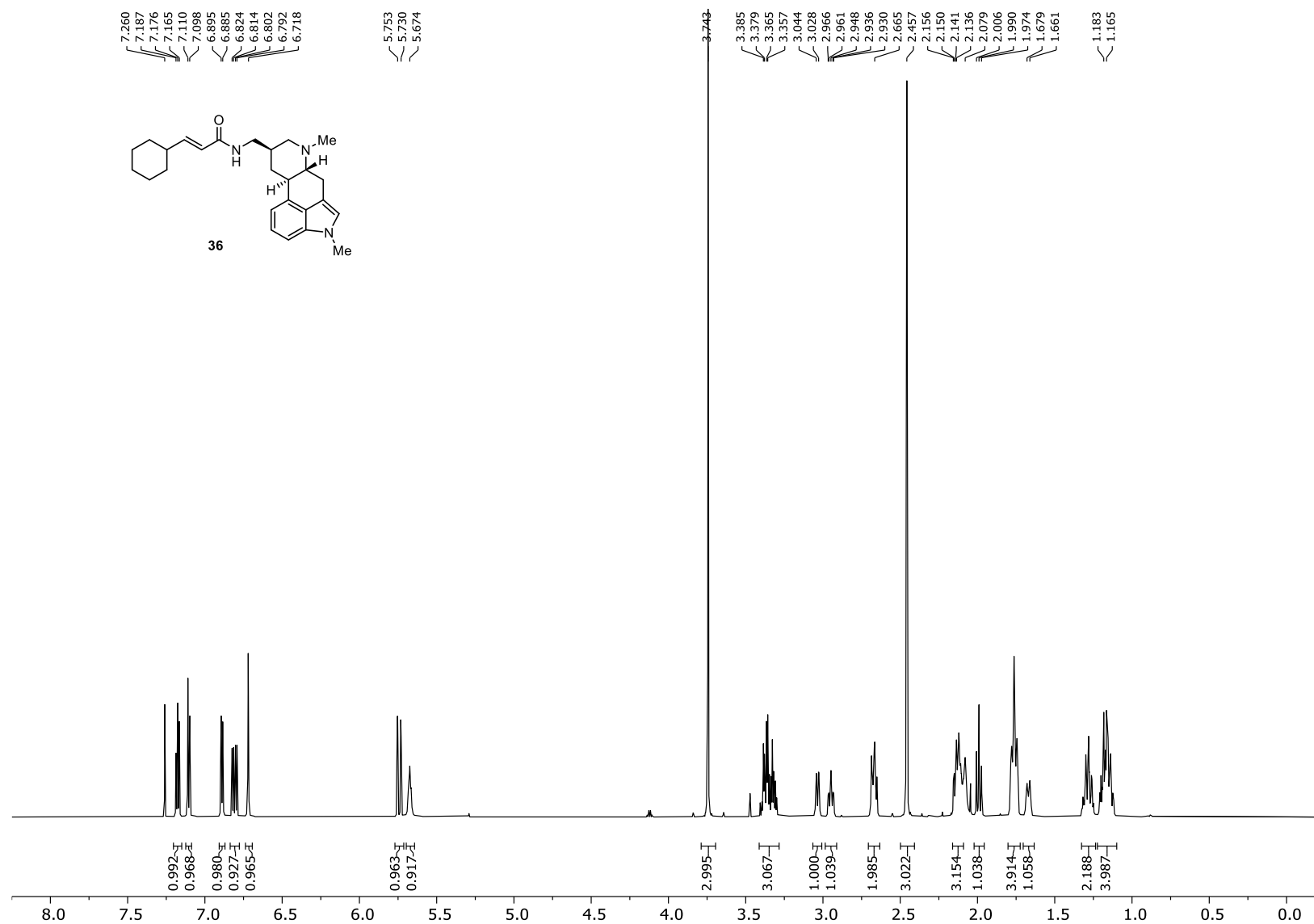
N-(3'-Cyclopentyl-*trans*-acryloyl) ergoline derivative (**35**) (^1H NMR; 700 MHz; CDCl_3)



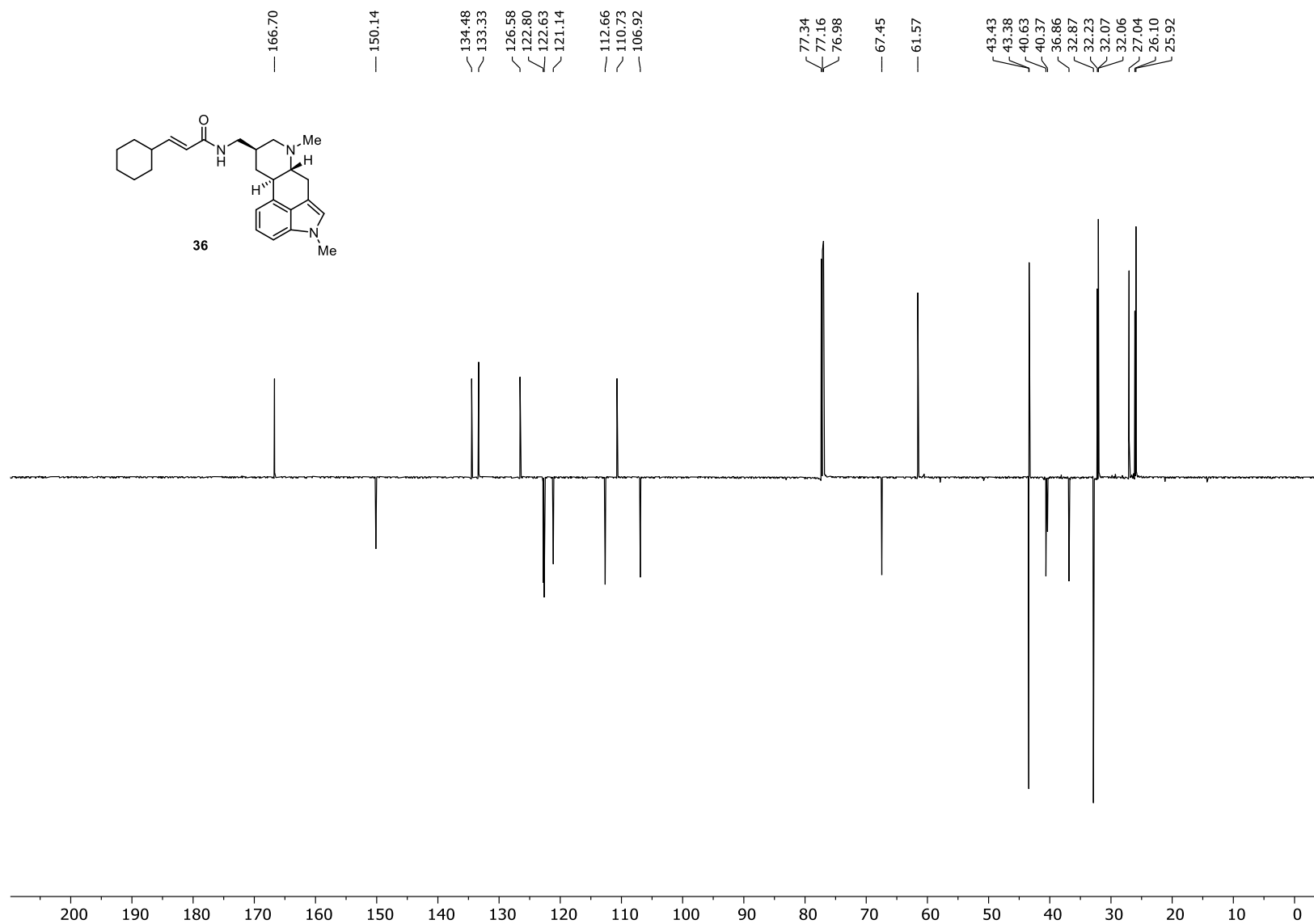
N-(3'-Cyclopentyl-*trans*-acryloyl) ergoline derivative (**35**) (^{13}C NMR; 175 MHz; CDCl_3)



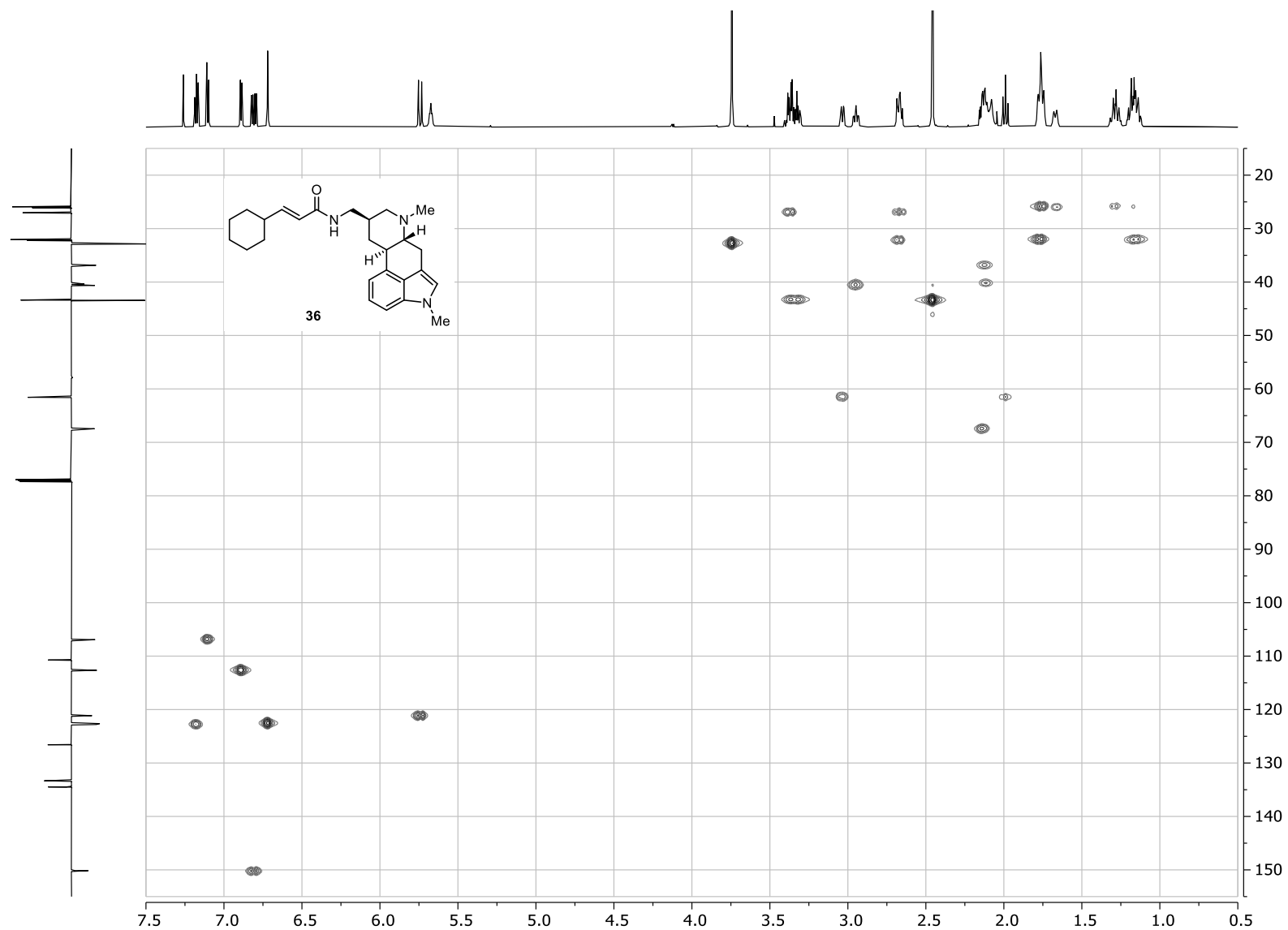
N-(3'-Cyclohexyl-*trans*-acryloyl) ergoline derivative (**36**) (¹H NMR; 700 MHz; CDCl₃)



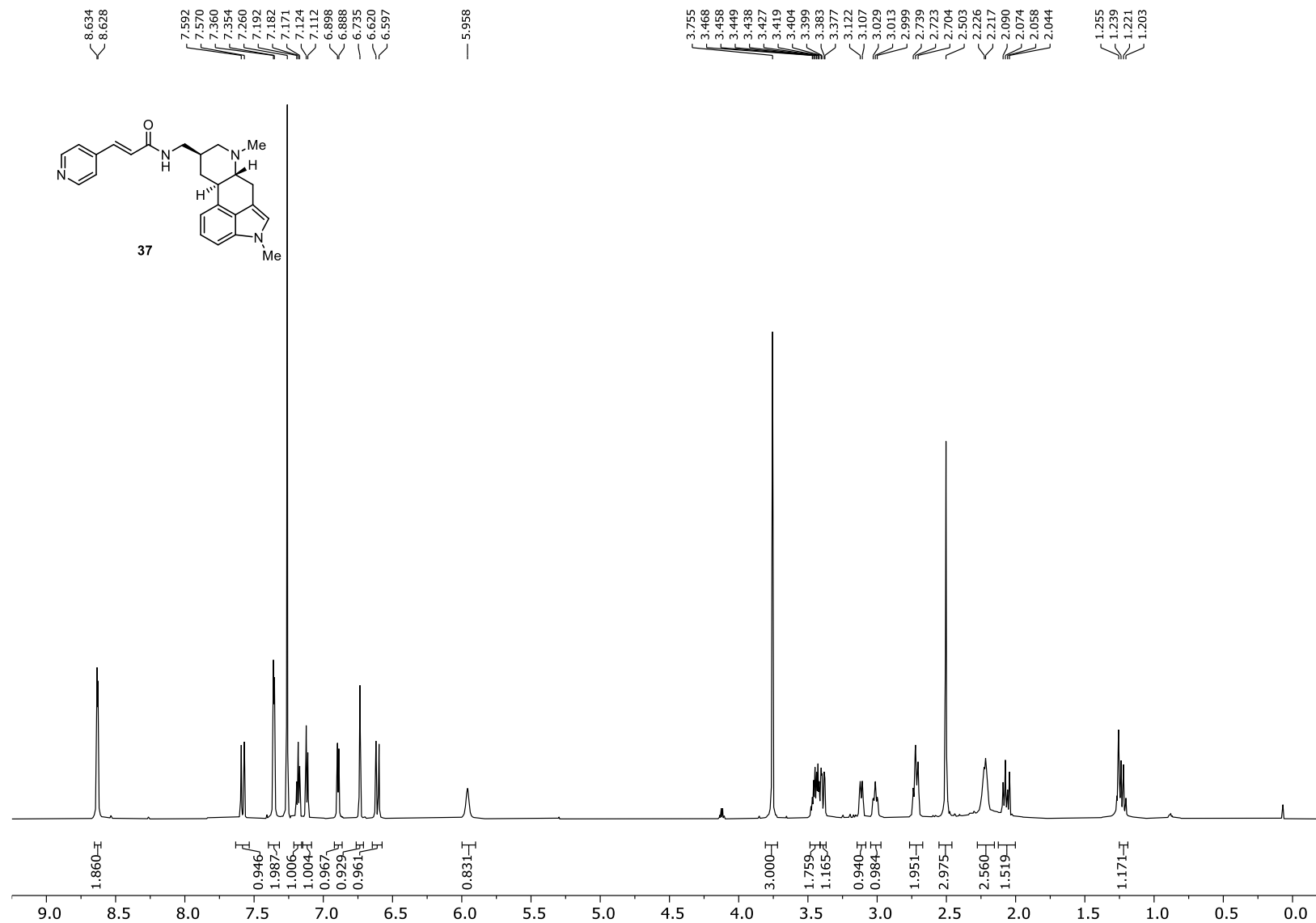
N-(3'-Cyclohexyl-*trans*-acryloyl) ergoline derivative (**36**) (^{13}C NMR; 175 MHz; CDCl_3)



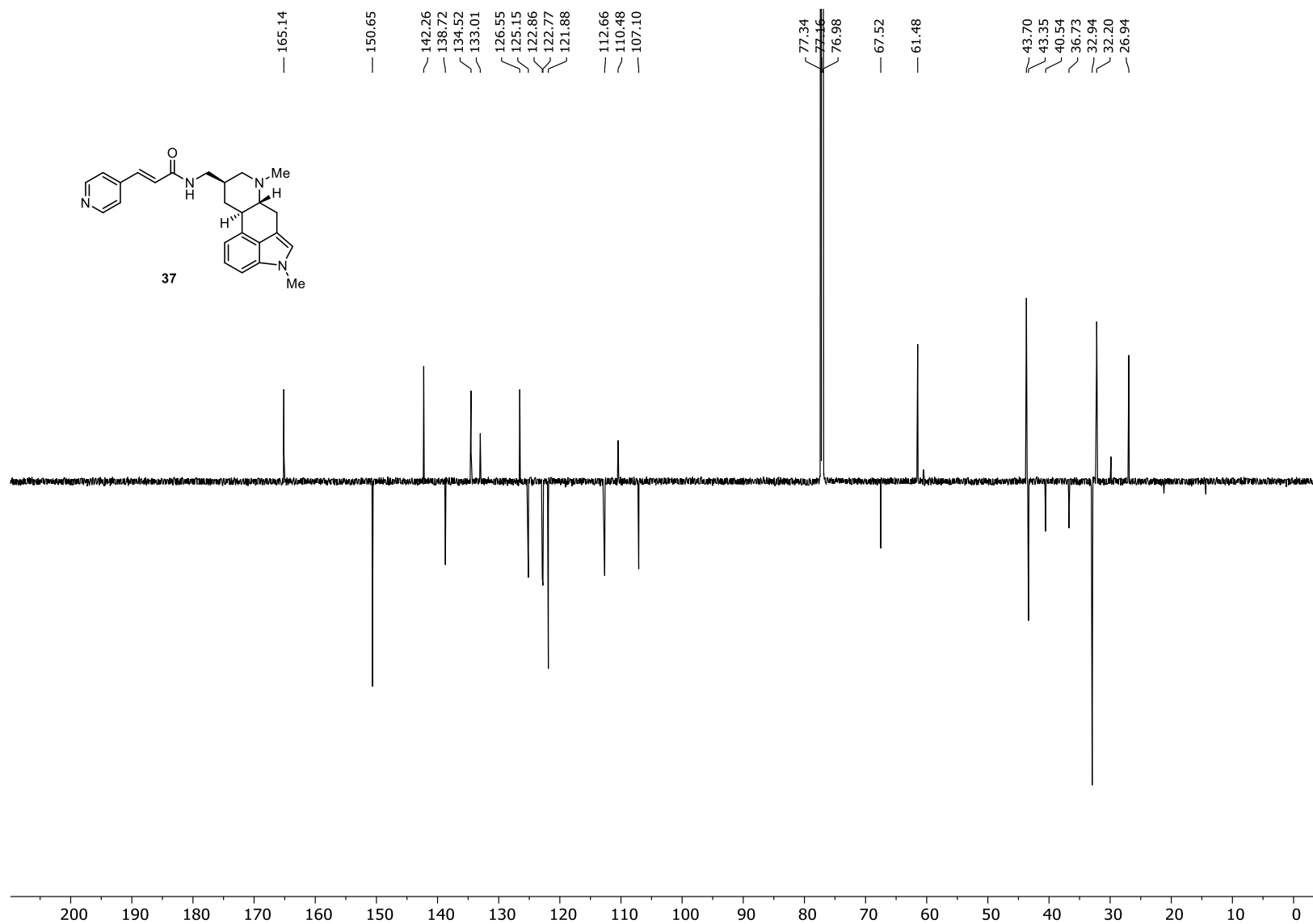
N-(3'-Cyclohexyl-*trans*-acryloyl) ergoline derivative (**36**) (HSQC; CDCl₃)



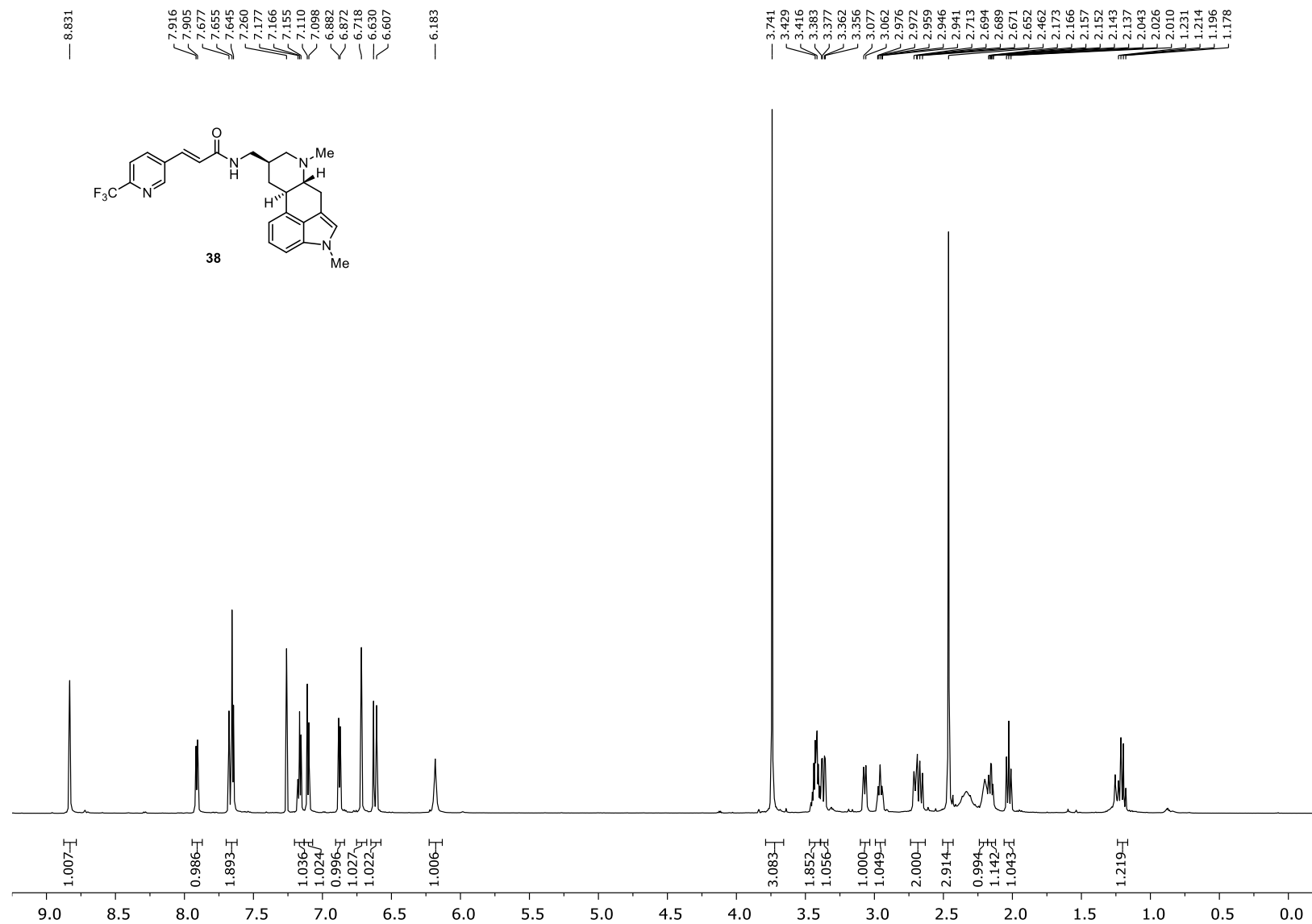
N-(3'-(4-Pyridyl)-*trans*-acryloyl) ergoline derivative (**37**) (^1H NMR; 700 MHz; CDCl_3)



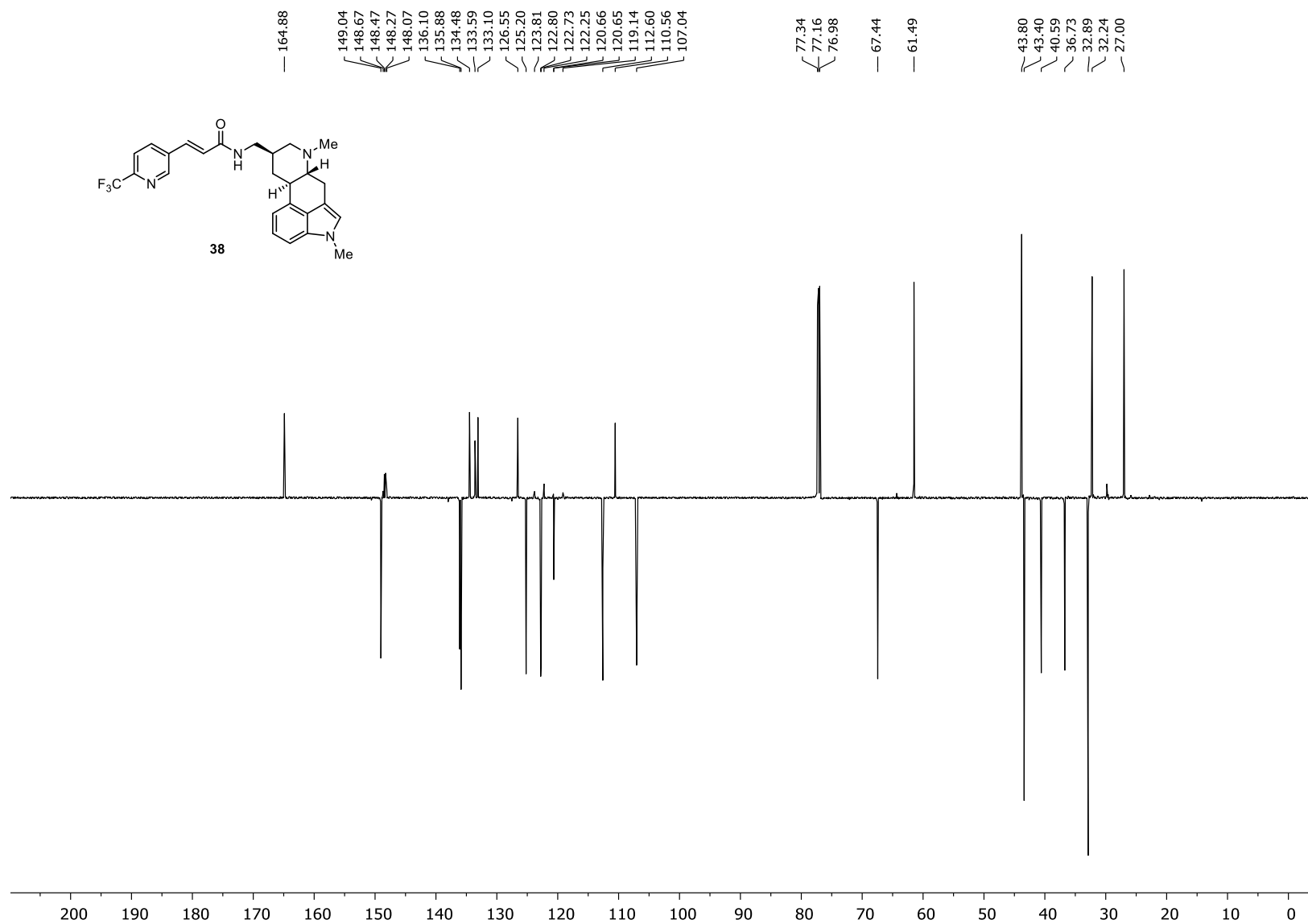
N-(3'-(4-Pyridyl)-*trans*-acryloyl) ergoline derivative (**37**) (^{13}C NMR; 175 MHz; CDCl_3)



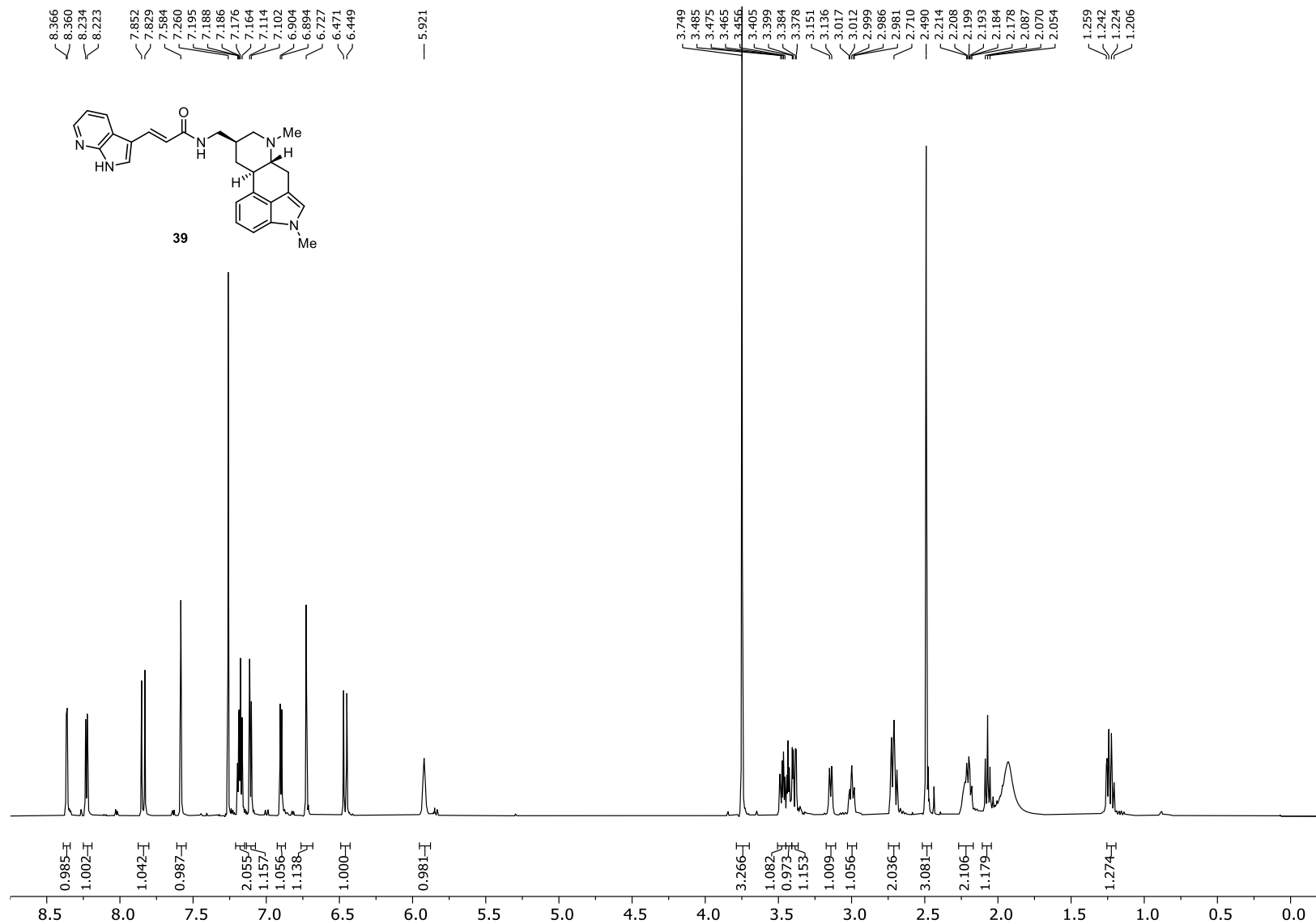
N-(3'-(4-Trifluoromethyl-3-pyridyl)-*trans*-acryloyl) ergoline derivative (**38**) (^1H NMR; 700 MHz; CDCl_3)



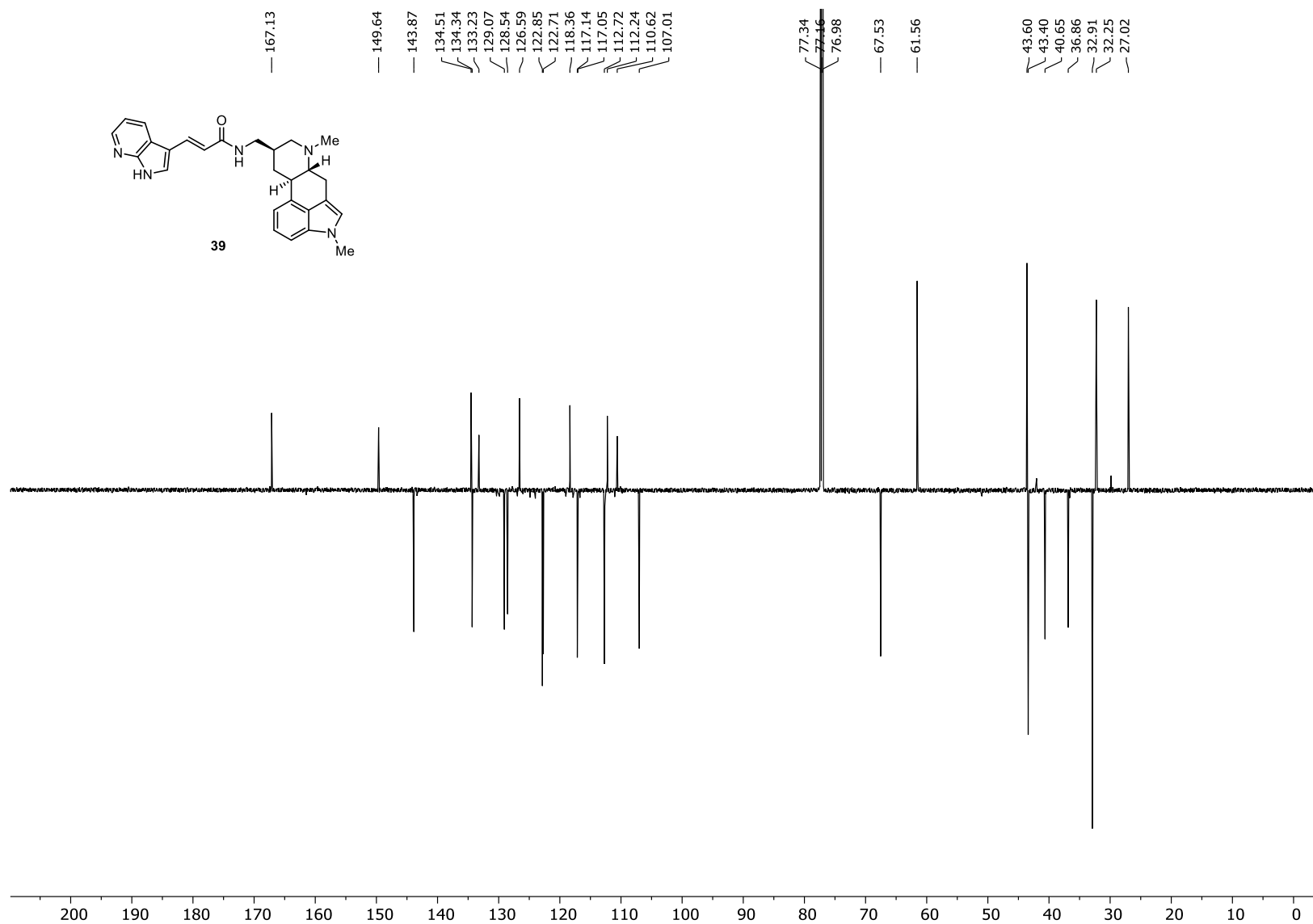
N-(3'-(4-Trifluoromethyl-3-pyridyl)-*trans*-acryloyl) ergoline derivative (**38**) (^{13}C NMR; 175 MHz; CDCl_3)



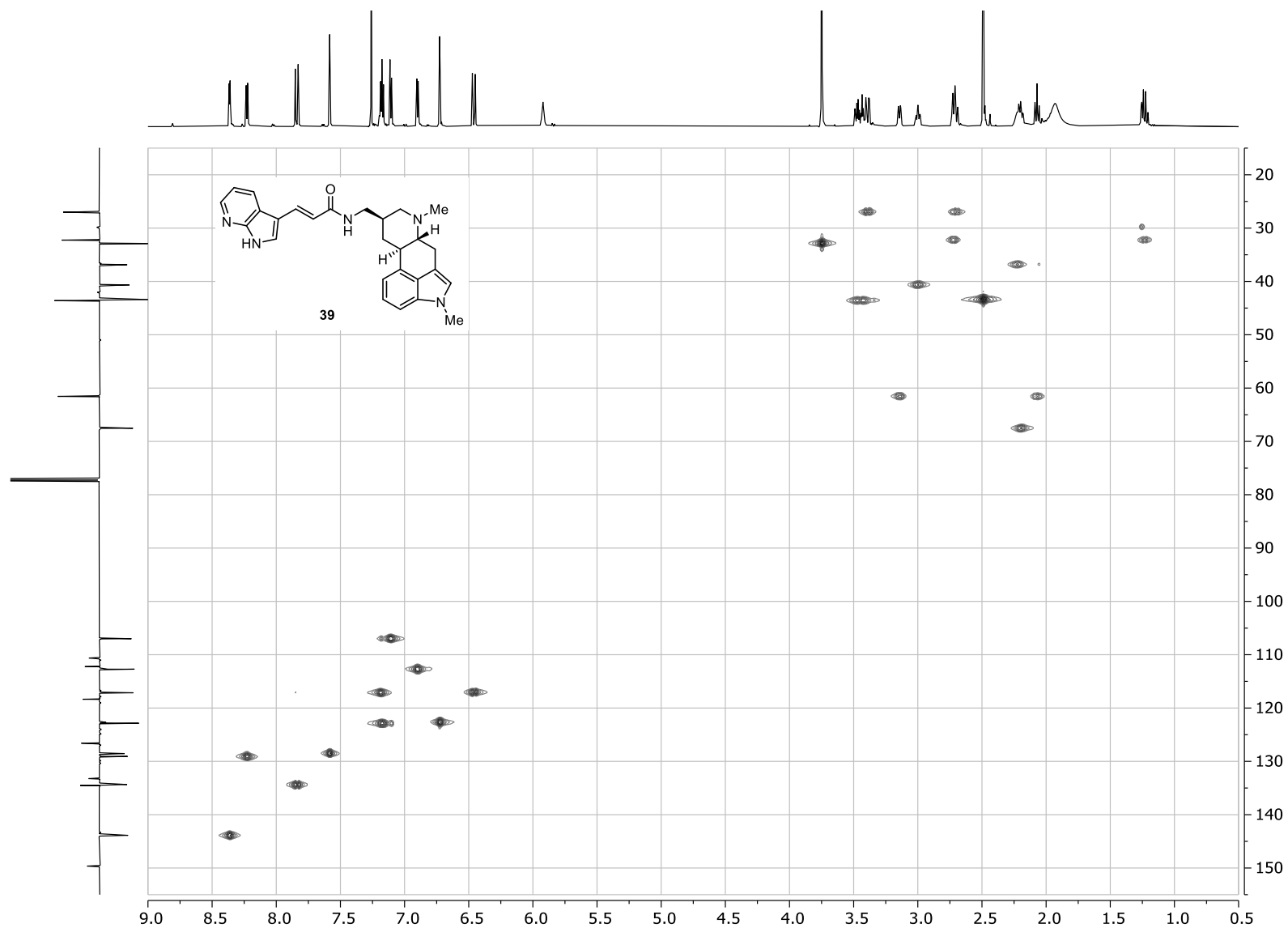
N-(3'-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*E*-acryloyl) ergoline derivative (**39**) (¹H NMR; 700 MHz; CDCl₃)



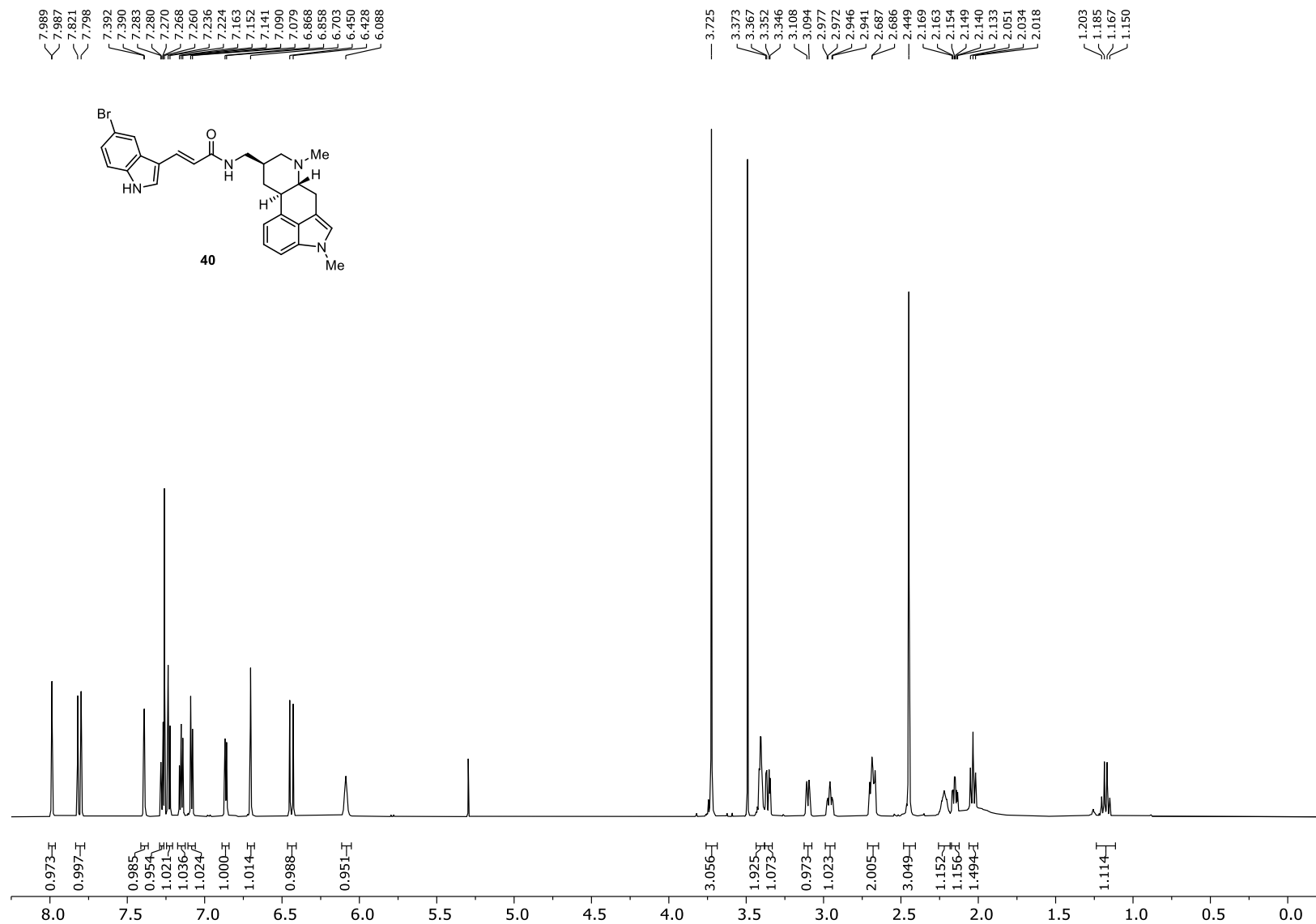
N-(3'-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*E*-acryloyl) ergoline derivative (**39**) (^{13}C NMR; 175 MHz; CDCl_3)



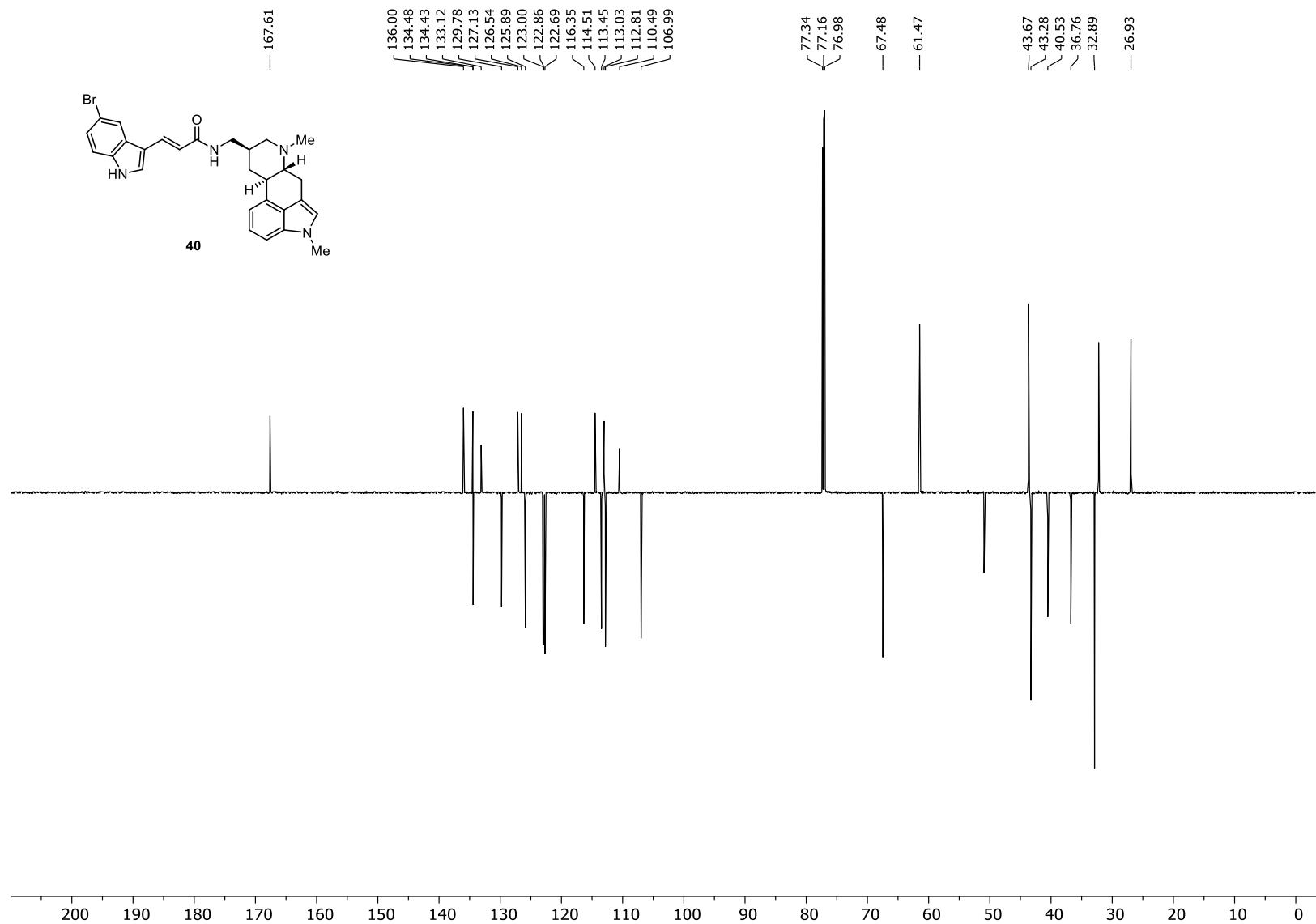
N-(3'-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-*E*-acryloyl) ergoline derivative (**39**) (HSQC; CDCl₃)



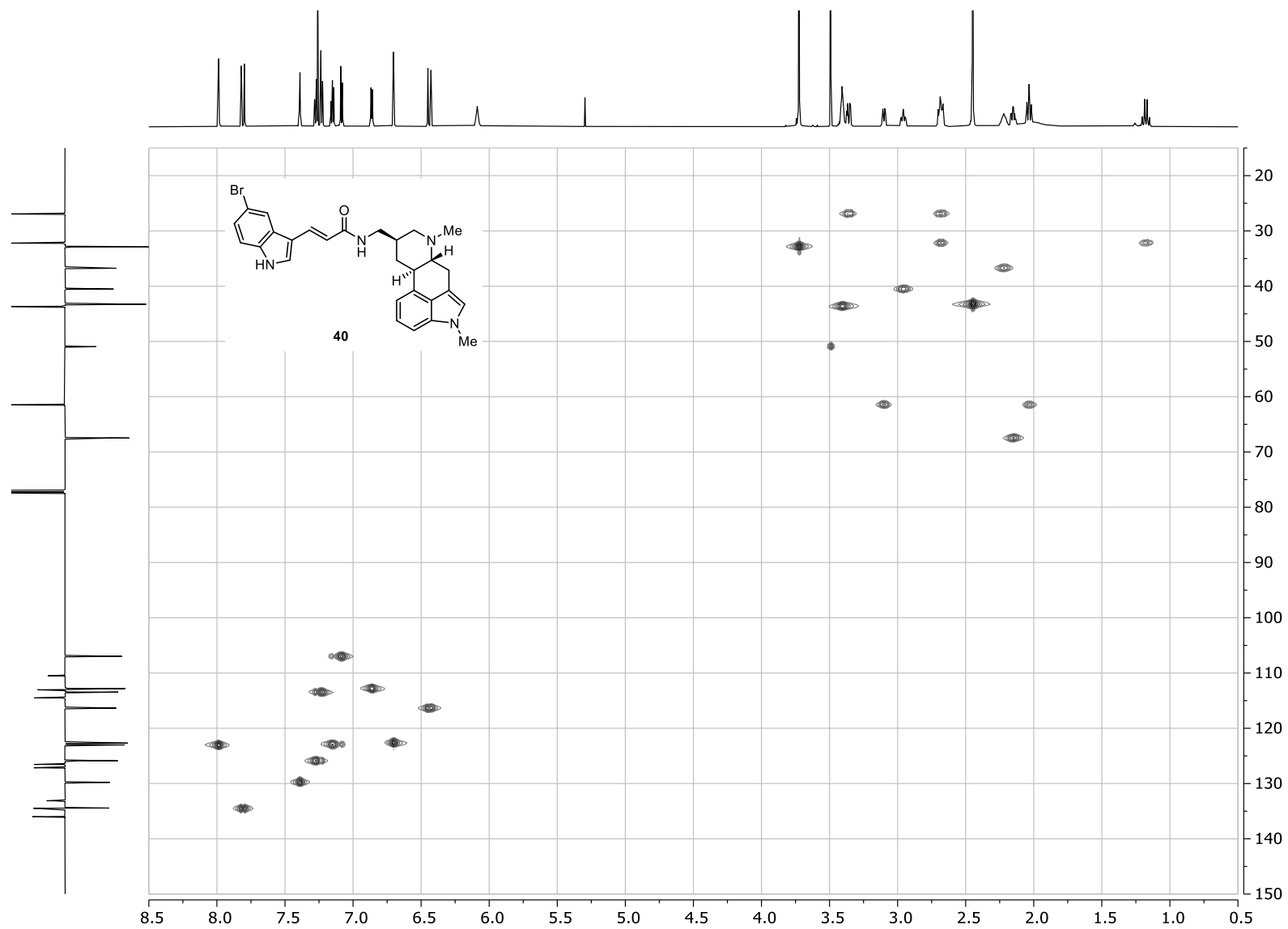
N-(3'-(5-Bromoindol-3-yl)-*E*-acryloyl) ergoline derivative (**40**) (^1H NMR; 700 MHz; CDCl_3)



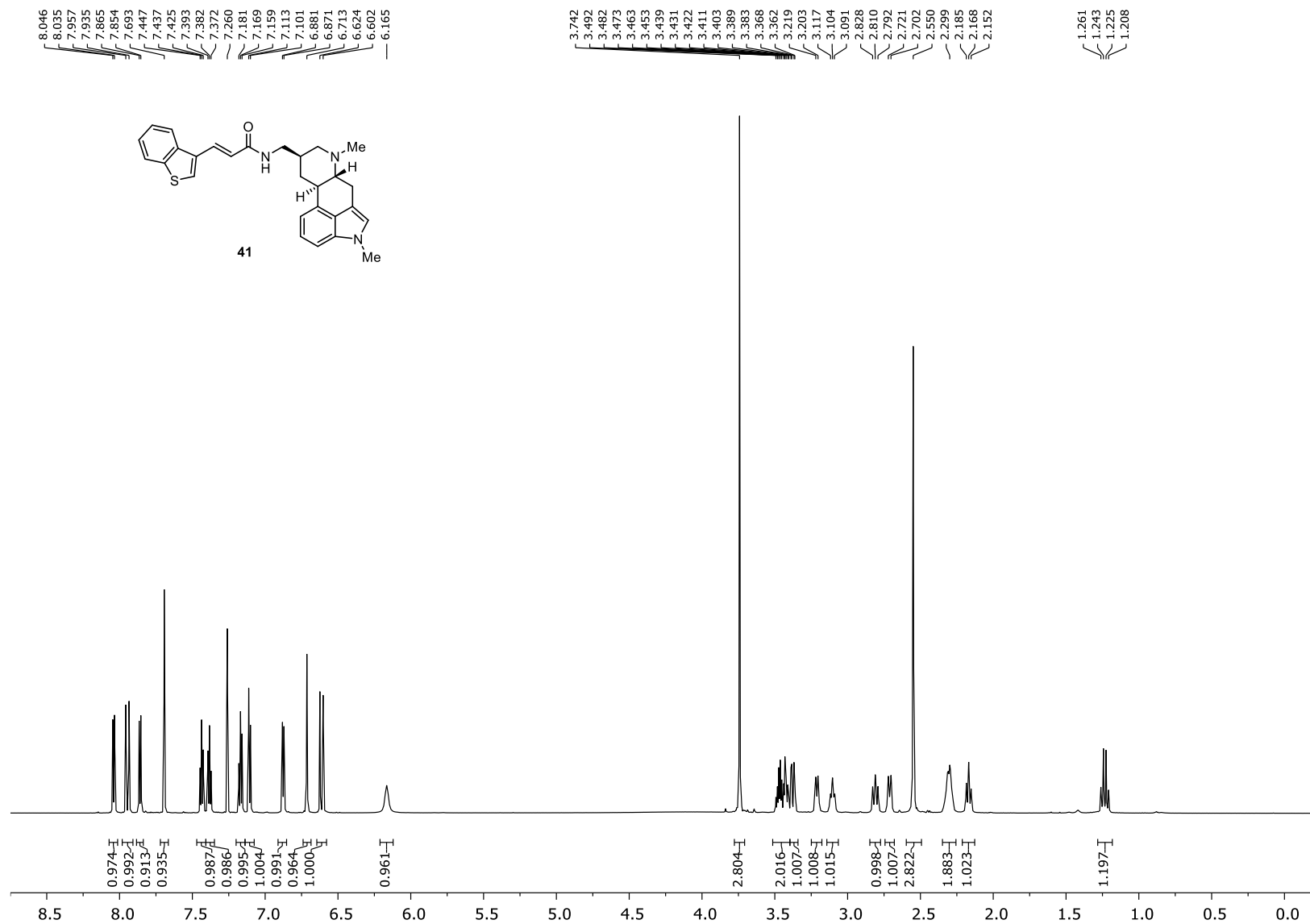
N-(3'-(5-Bromoindol-3-yl)-*E*-acryloyl) ergoline derivative (**40**) (^{13}C NMR; 175 MHz; CDCl_3)



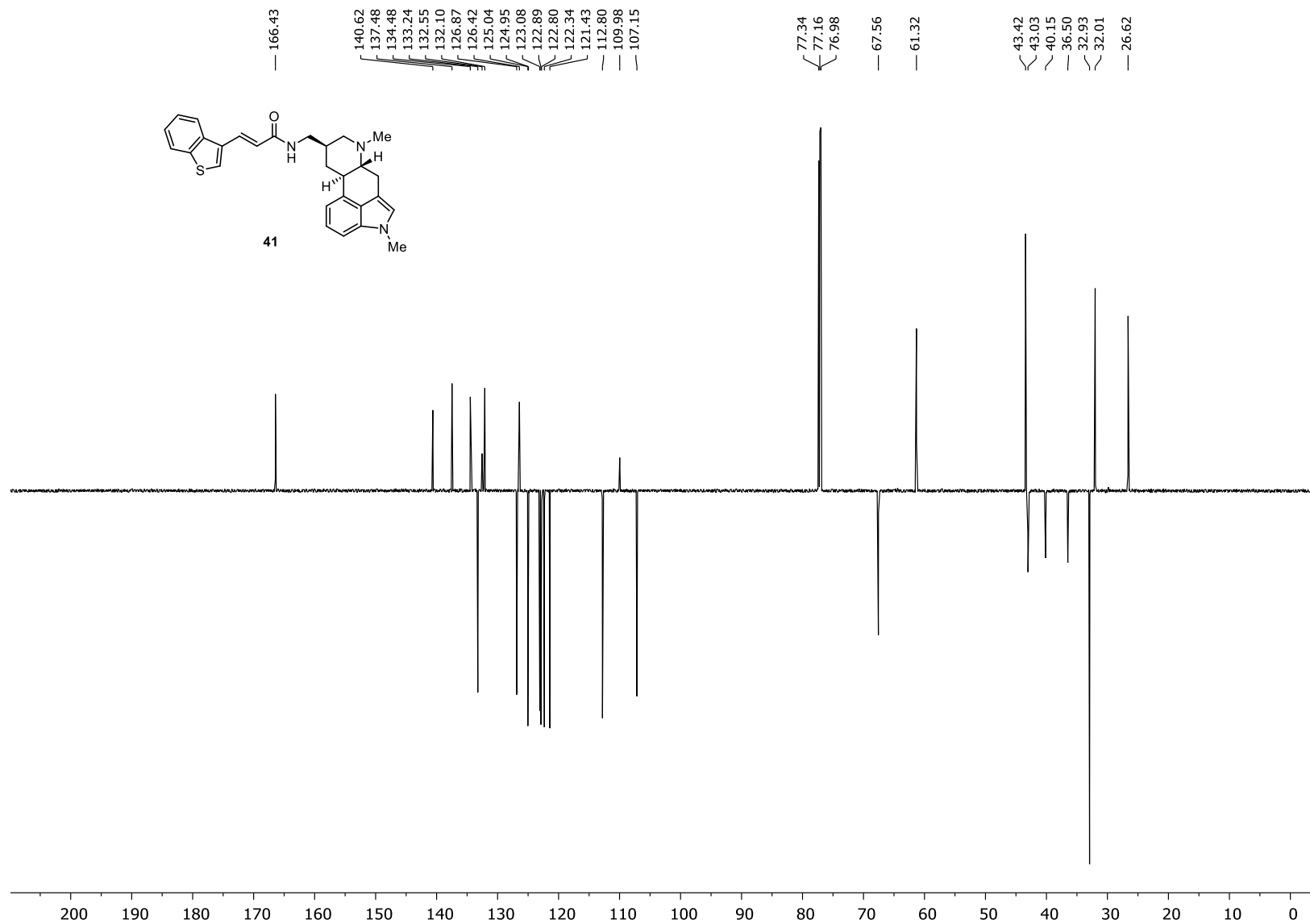
N-(3'-(5-Bromoindol-3-yl)-*E*-acryloyl) ergoline derivative (**40**) (HSQC; CDCl₃)



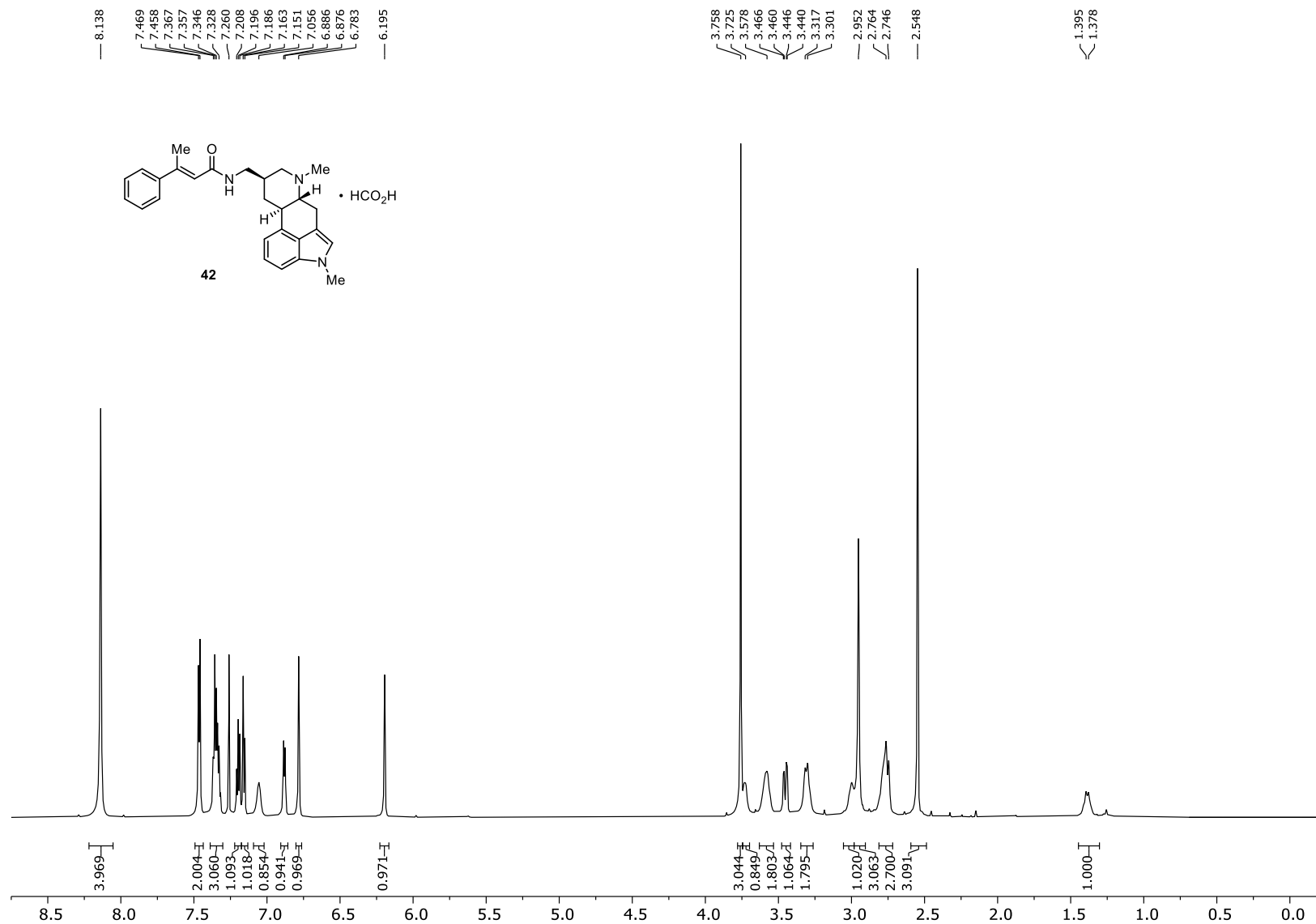
N-(3'-(3-Benzothiophenyl)-*E*-acryloyl) ergoline derivative (**41**) (¹H NMR; 700 MHz; CDCl₃)



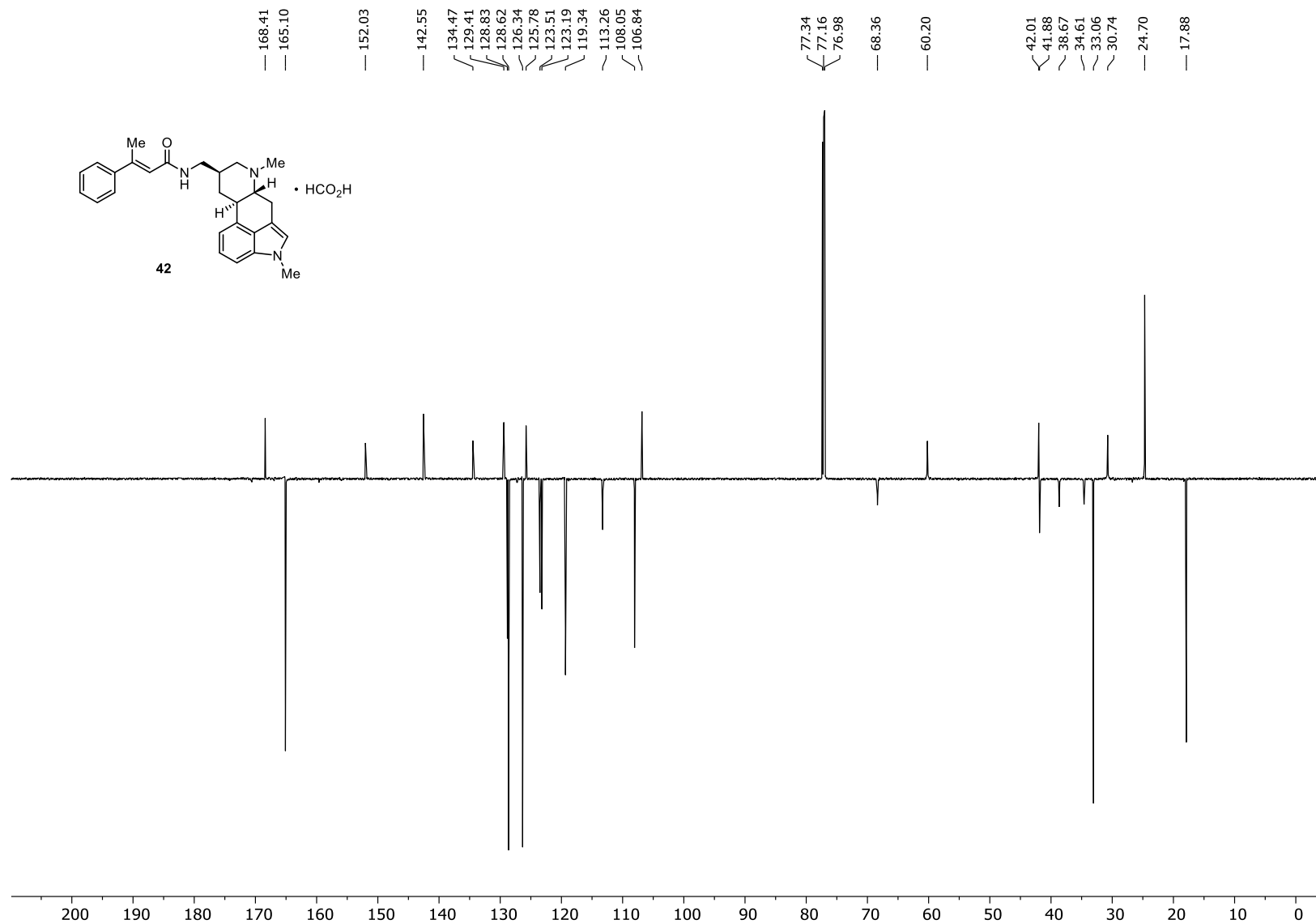
N-(3'-(3-Benzothiophenyl)-*E*-acryloyl) ergoline derivative (**41**) (^{13}C NMR; 175 MHz; CDCl_3)



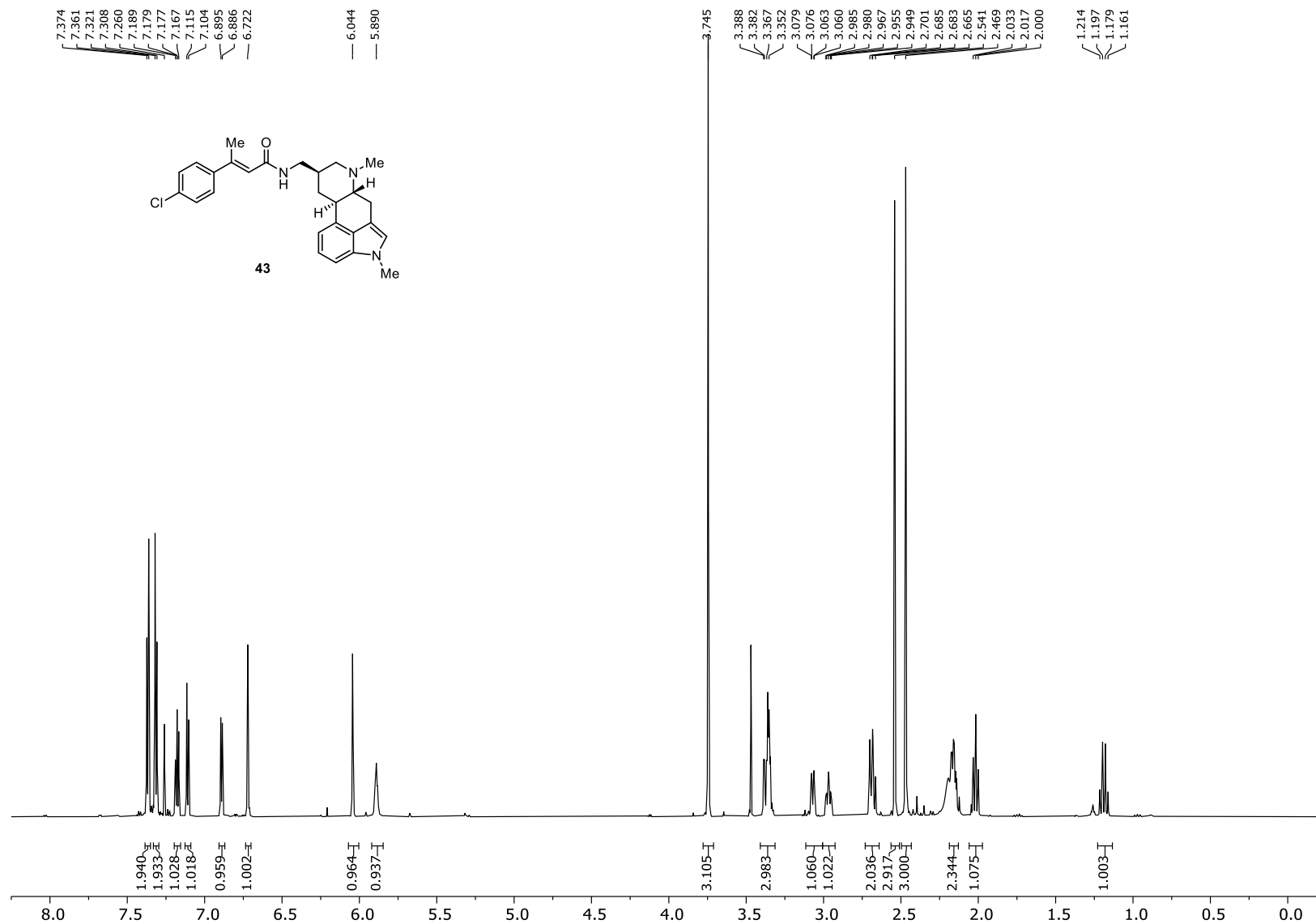
N-(*E*-3-Phenylbut-2-enoyl) ergoline derivative (**42**) (^1H NMR; 700 MHz; CDCl_3)



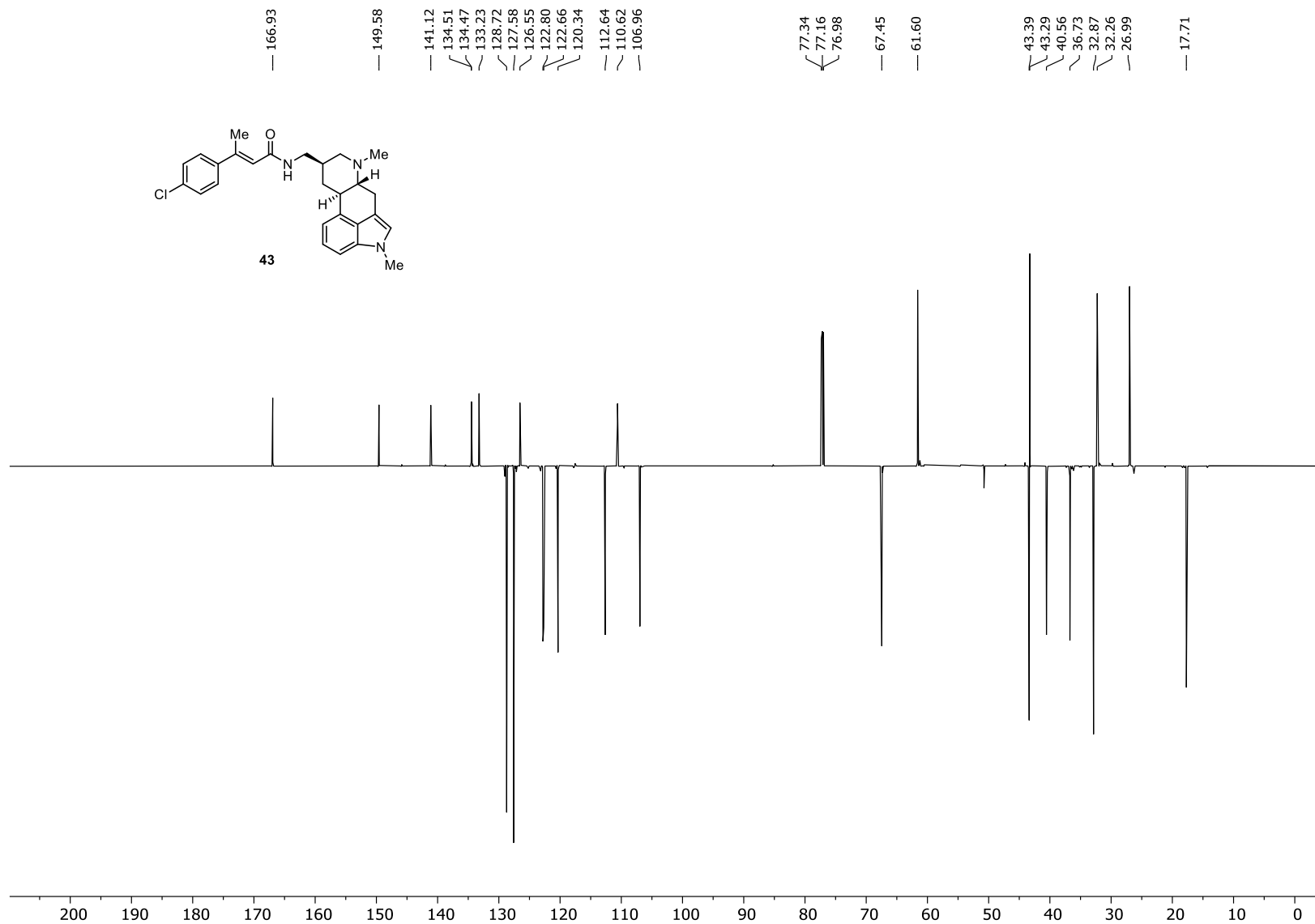
N-(*E*-3-Phenylbut-2-enoyl) ergoline derivative (**42**) (^{13}C NMR; 175 MHz; CDCl_3)



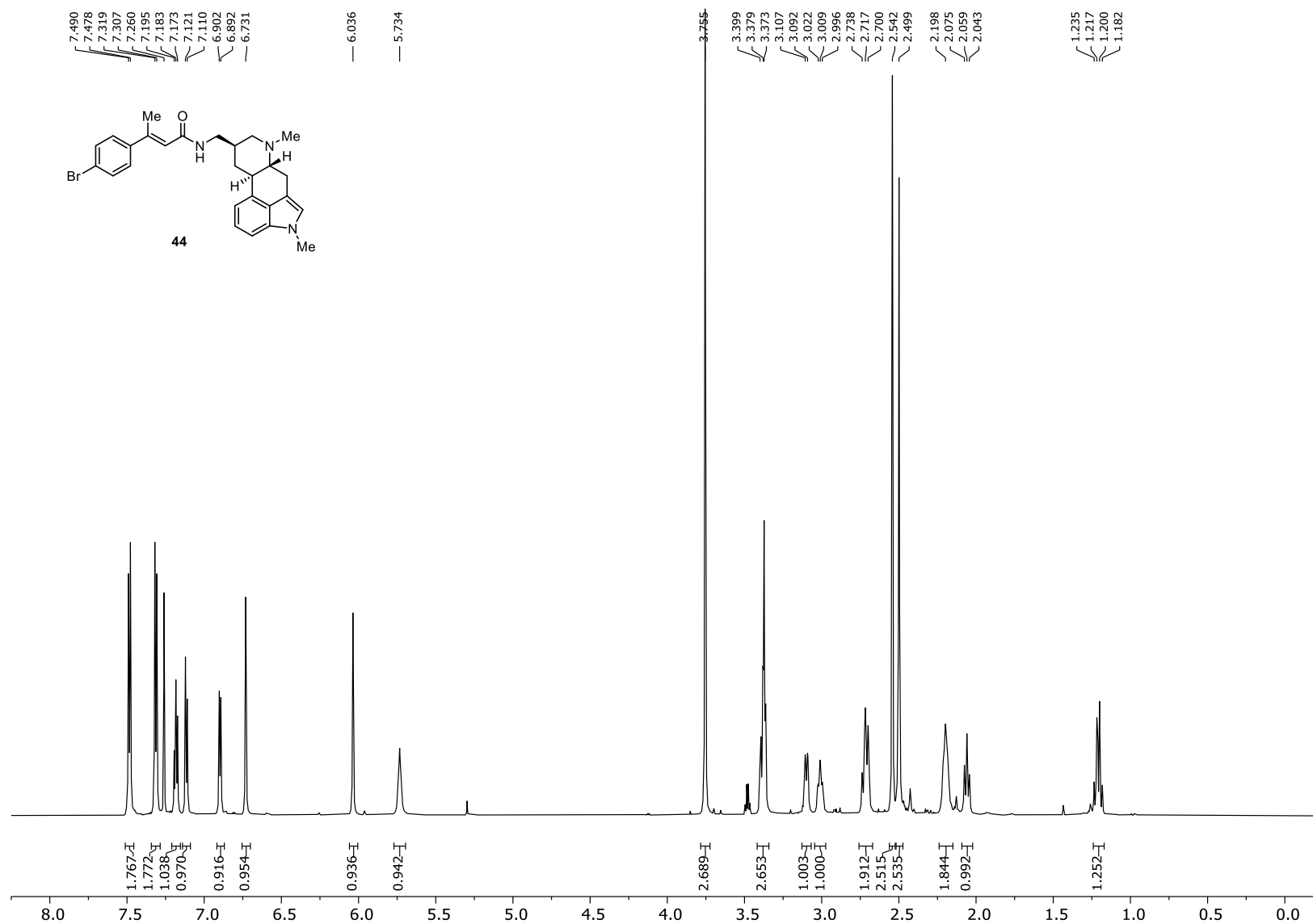
N-((*E*)-3-(4-Chlorophenyl)but-2-enoyl) ergoline derivative (**43**) (^1H NMR; 700 MHz; CDCl_3)



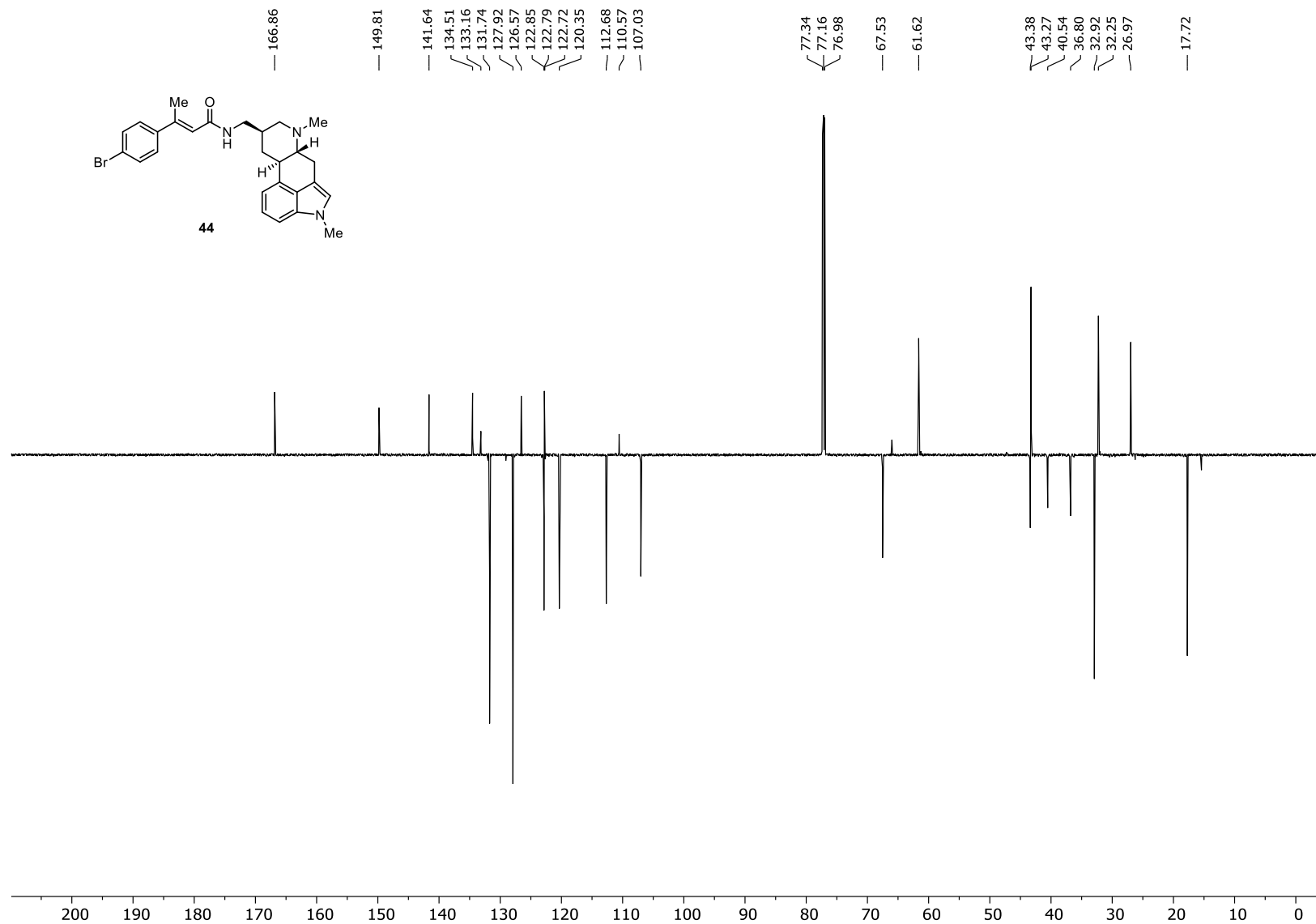
N-((*E*)-3-(4-Chlorophenyl)but-2-enoyl) ergoline derivative (**43**) (^{13}C NMR; 175 MHz; CDCl_3)



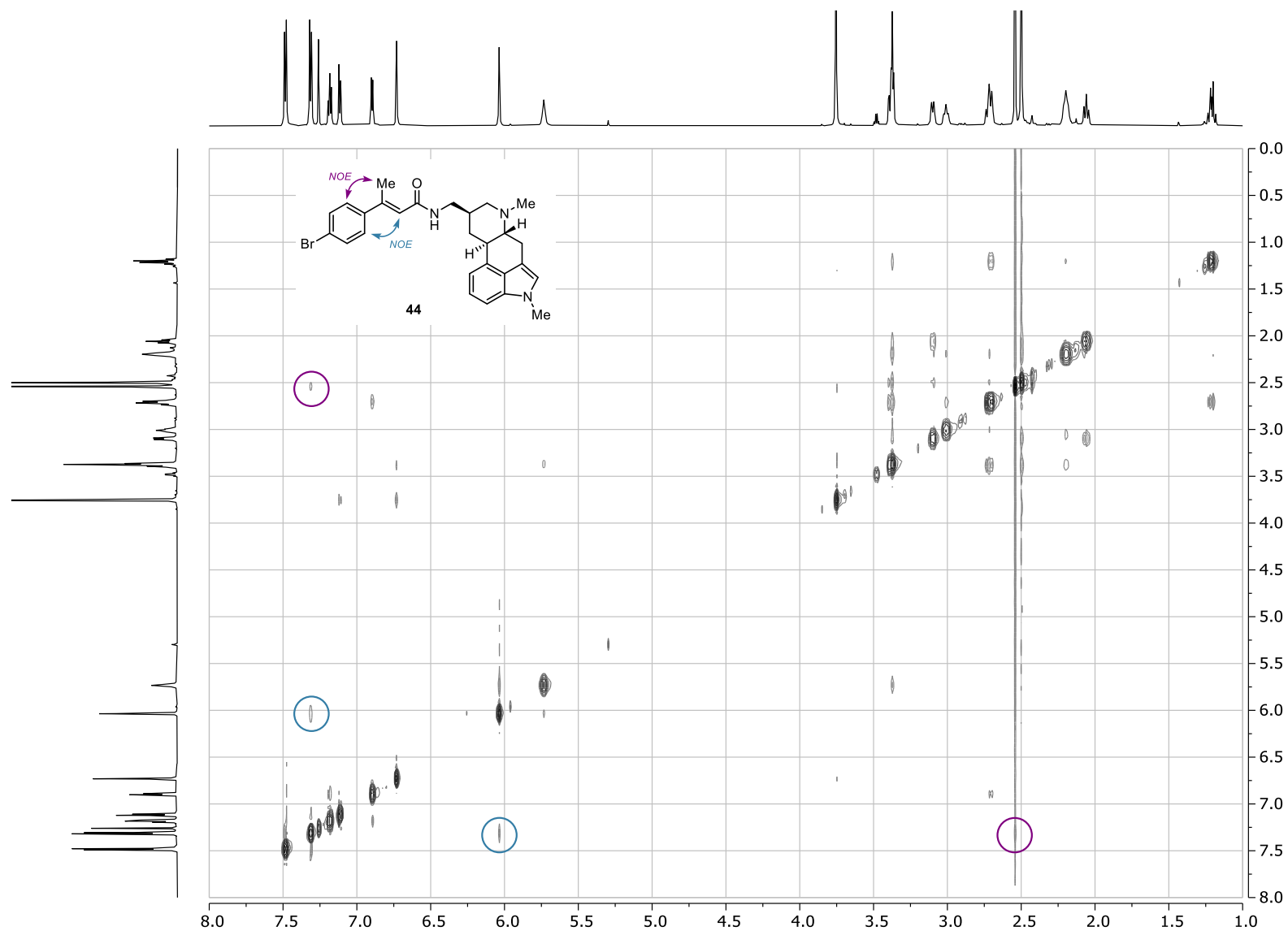
N-((*E*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**44**) (^1H NMR; 700 MHz; CDCl_3)



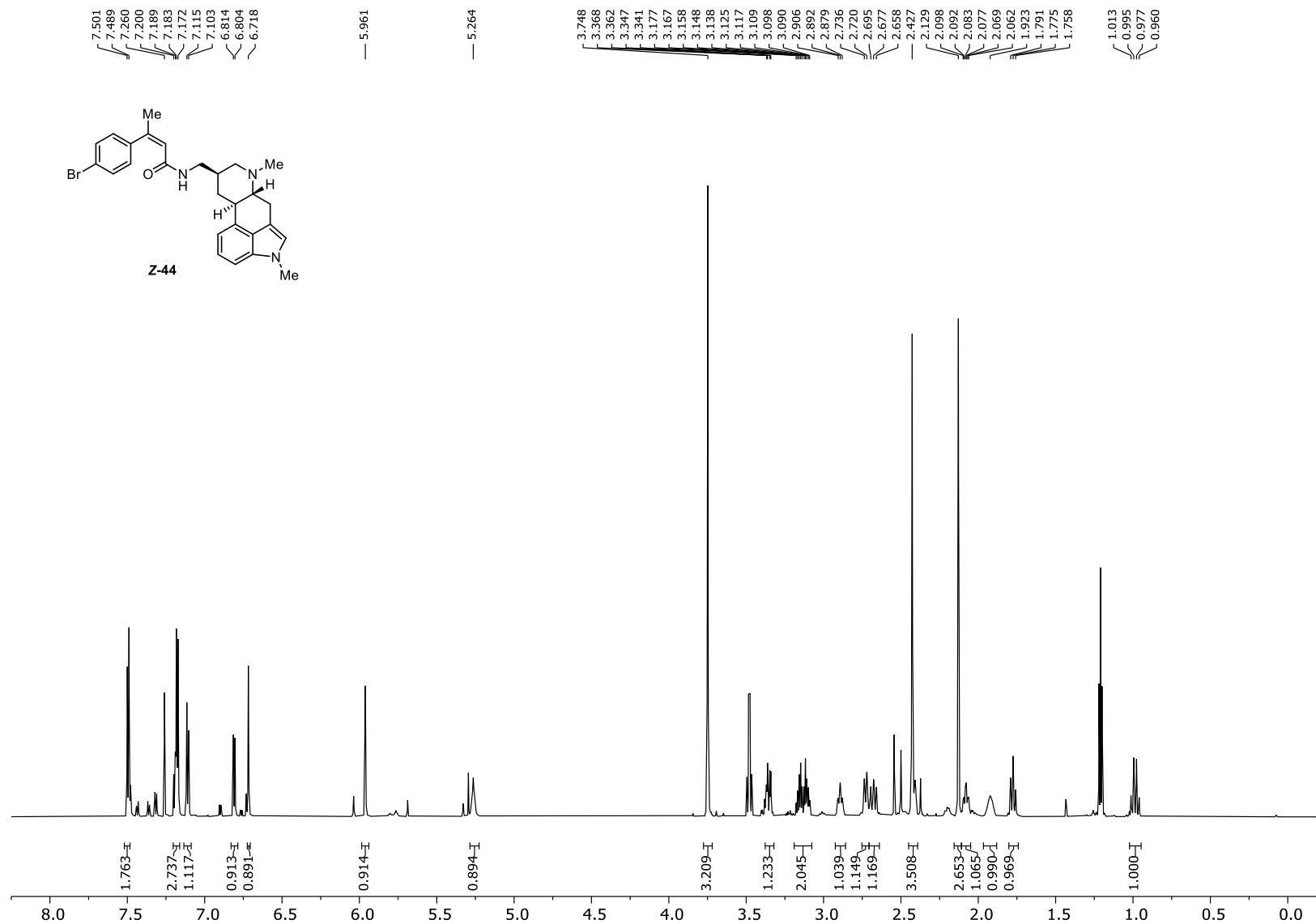
N-((*E*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**44**) (^{13}C NMR; 175 MHz; CDCl_3)



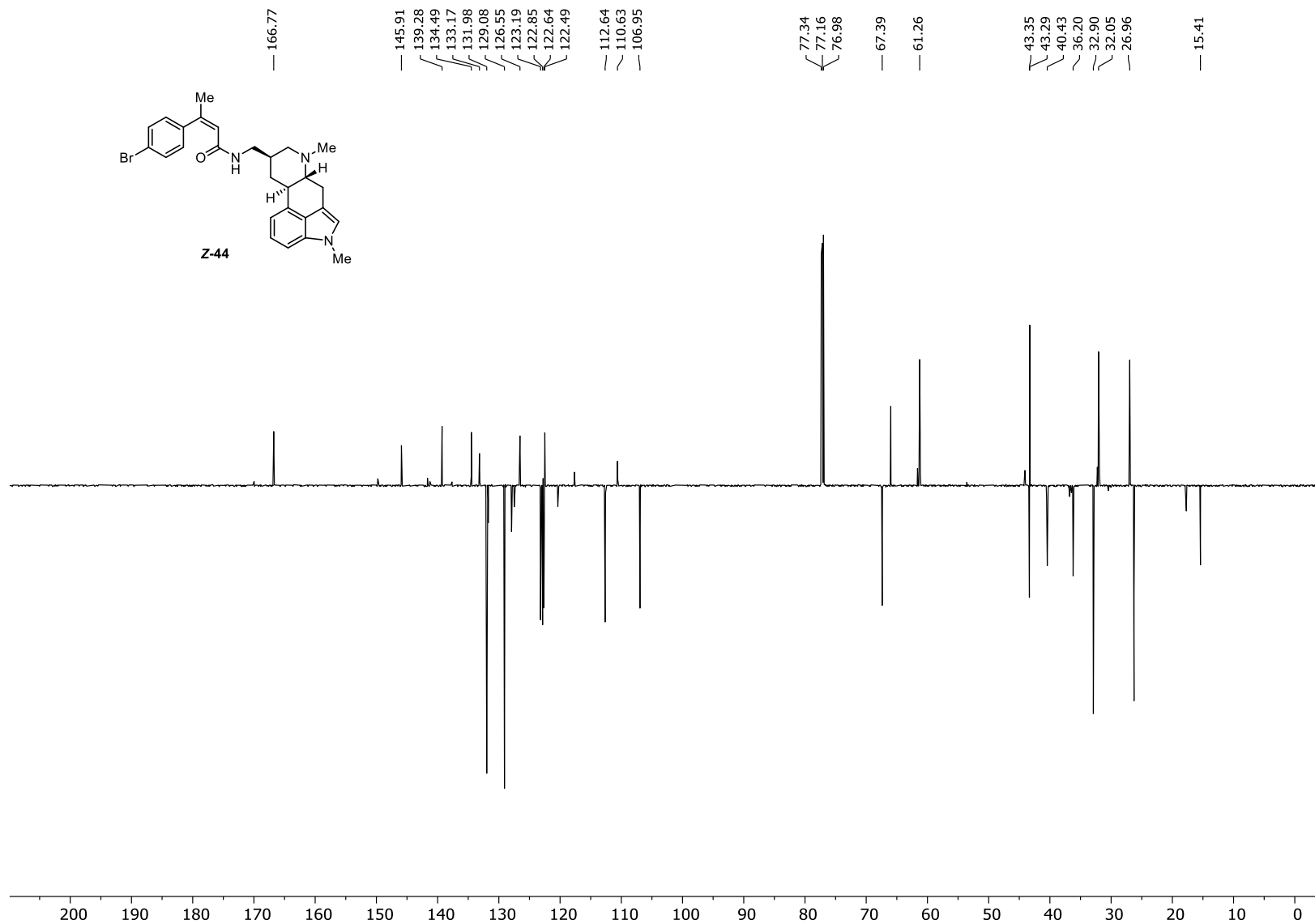
N-((*E*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**44**) (NOESY; CDCl₃)



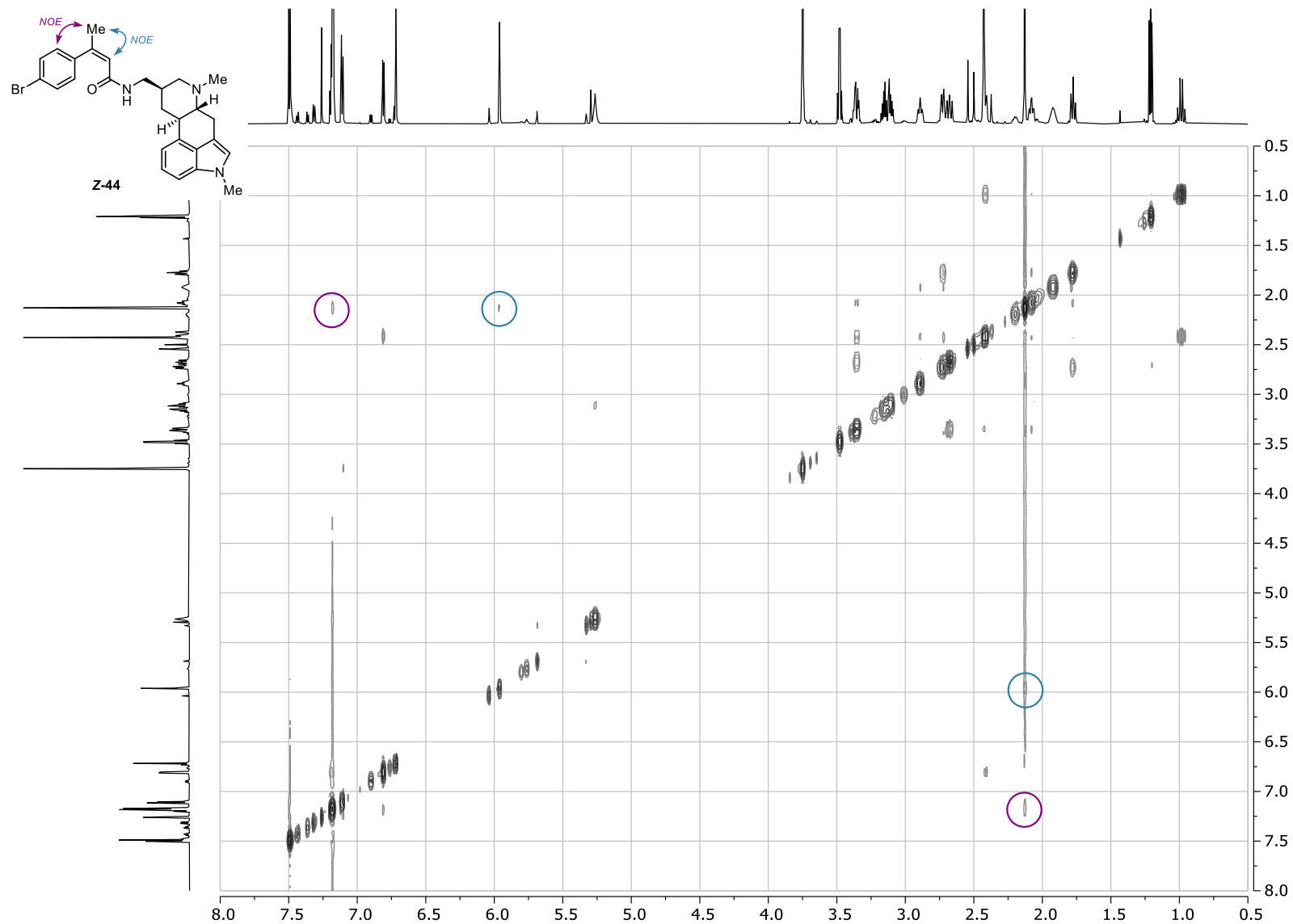
N-((*Z*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**Z-44**) (^1H NMR; 700 MHz; CDCl_3)



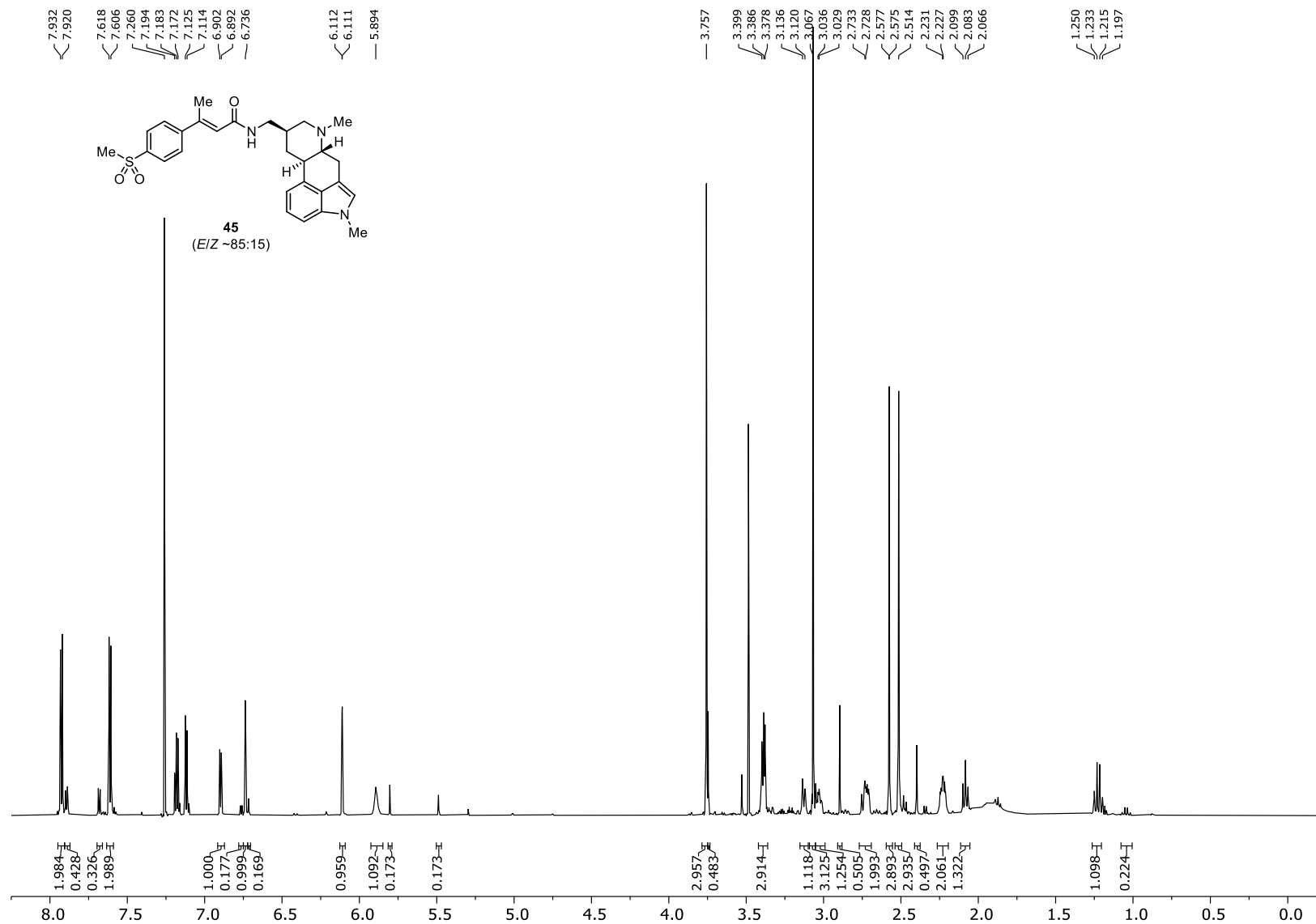
N-((*Z*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**Z-44**) (^{13}C NMR; 175 MHz; CDCl_3)



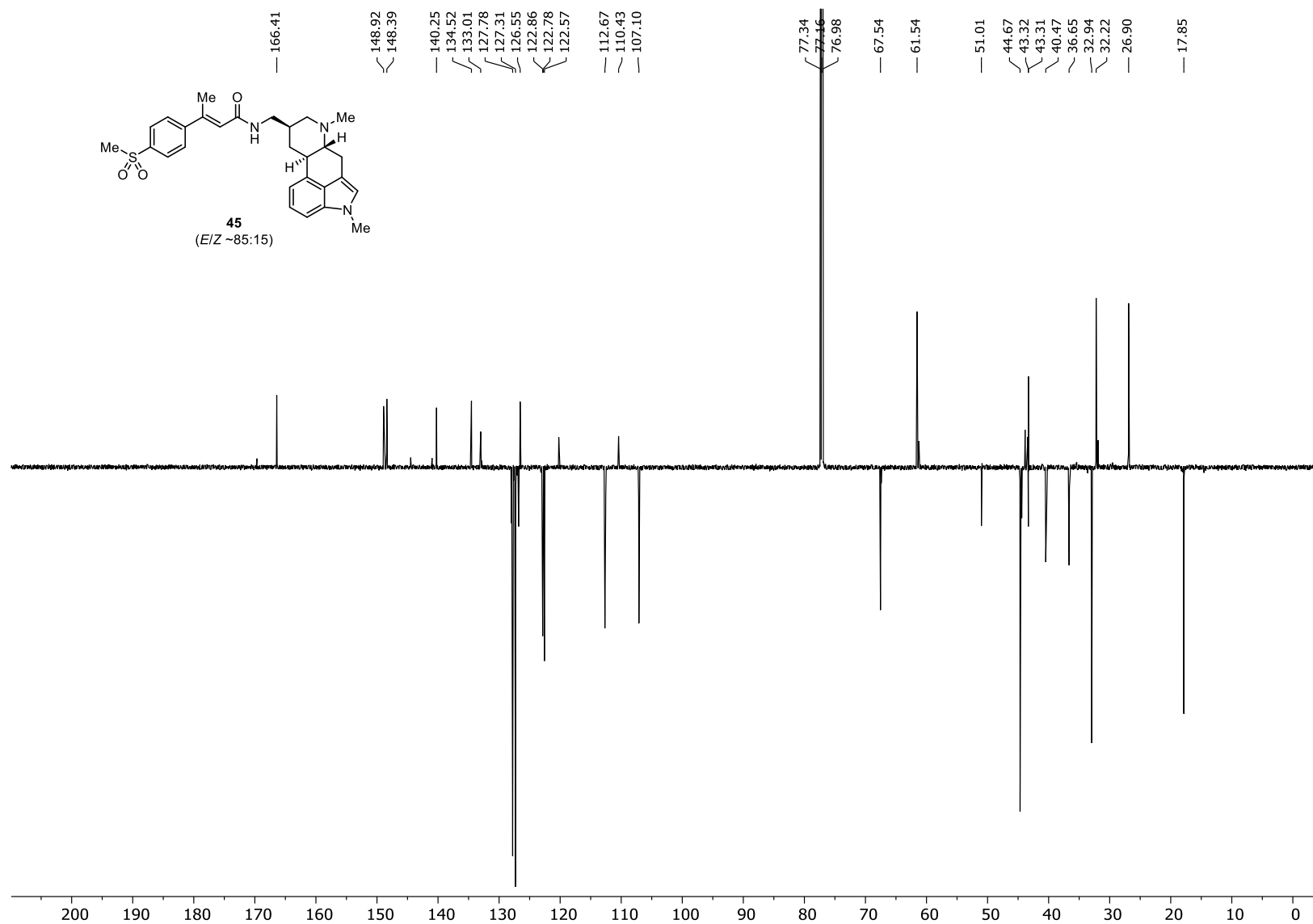
N-((*Z*)-3-(4-Bromophenyl)but-2-enoyl) ergoline derivative (**Z-44**) (NOESY; CDCl₃)



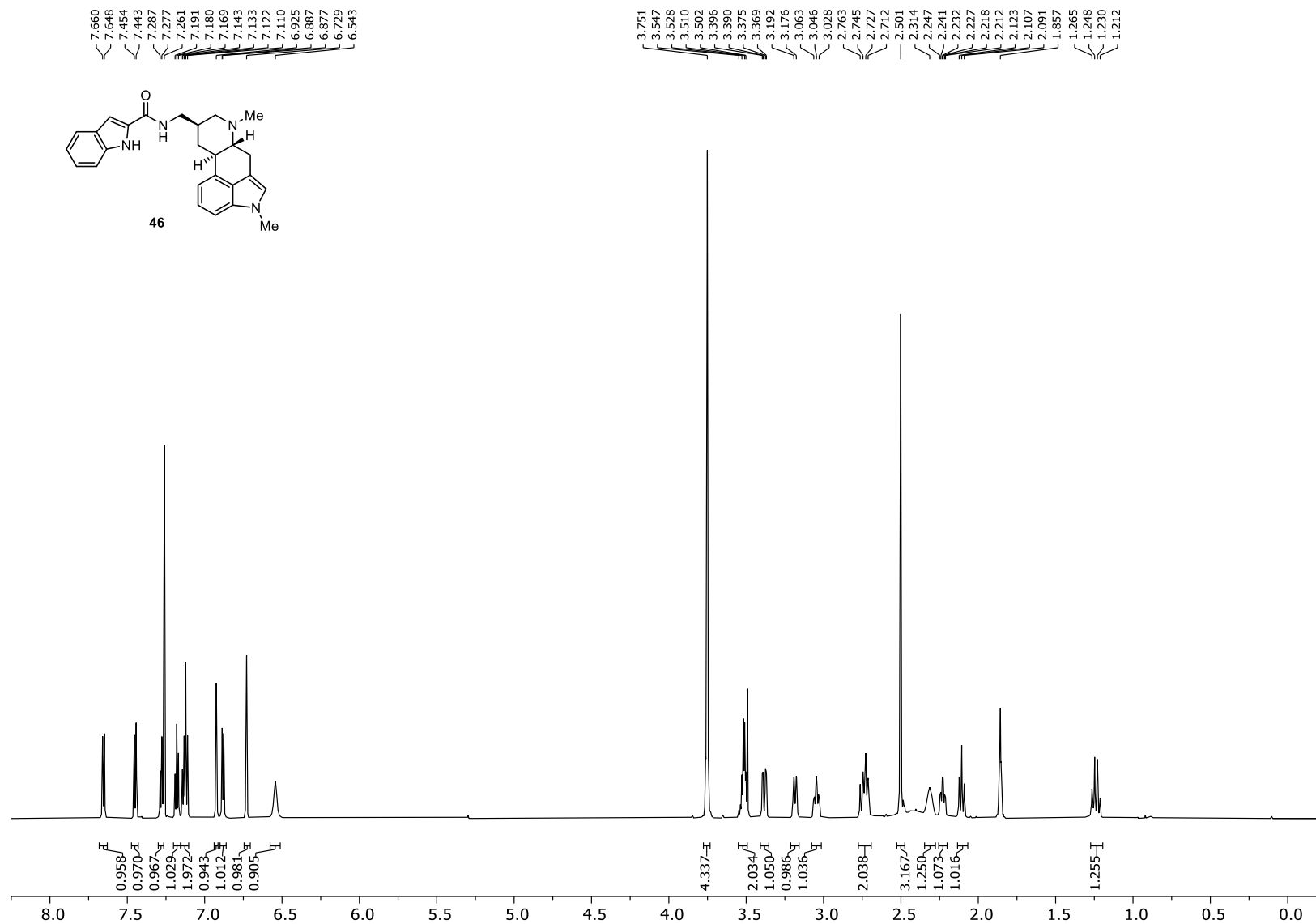
N-((*E*)-3-(4-Methylsulfonylphenyl)but-2-enoyl) ergoline derivative (**45**) (^1H NMR; 700 MHz; CDCl_3)



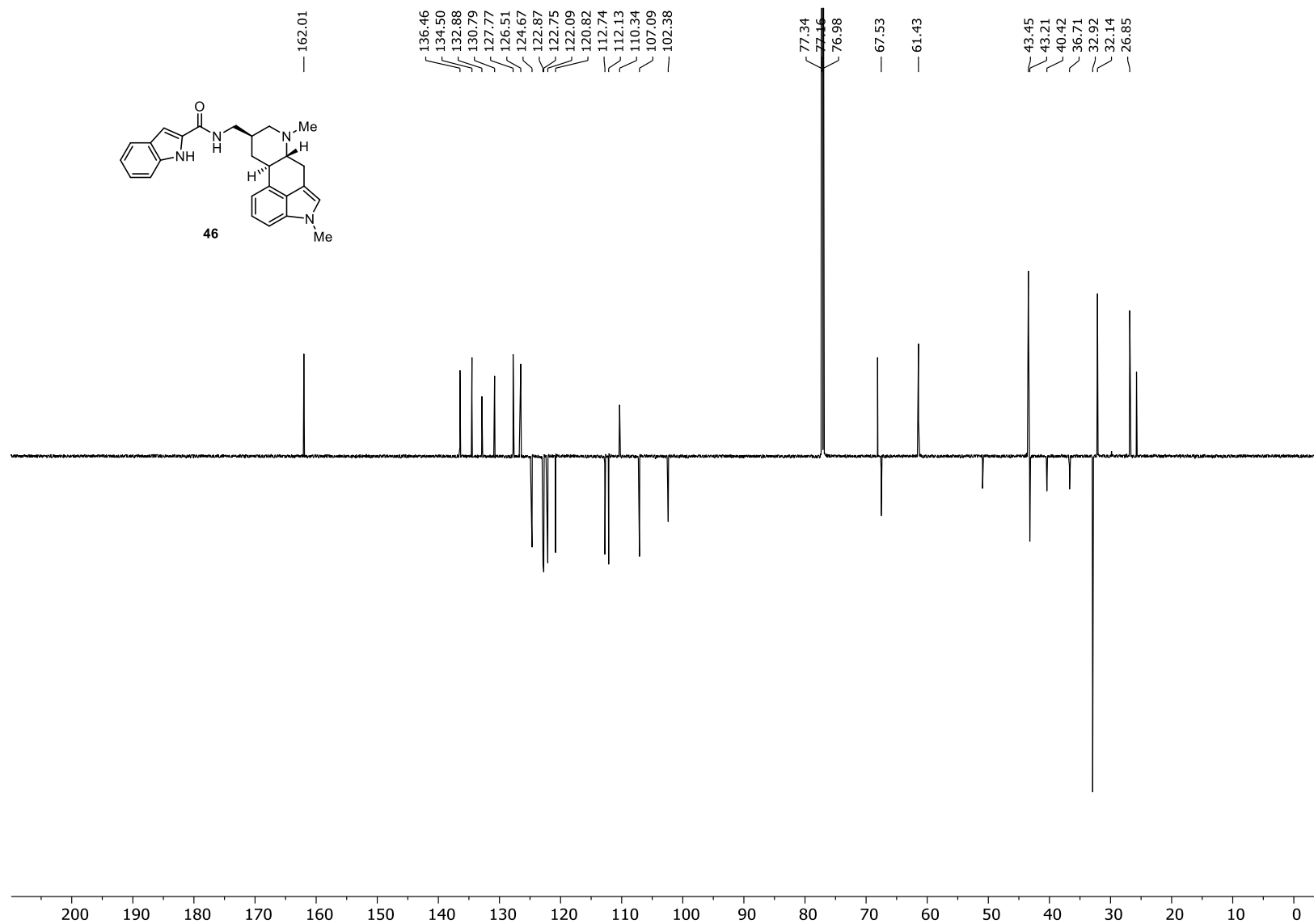
N-((*E*)-3-(4-Methylsulfonylphenyl)but-2-enoyl) ergoline derivative (**45**) (^{13}C NMR; 175 MHz; CDCl_3)



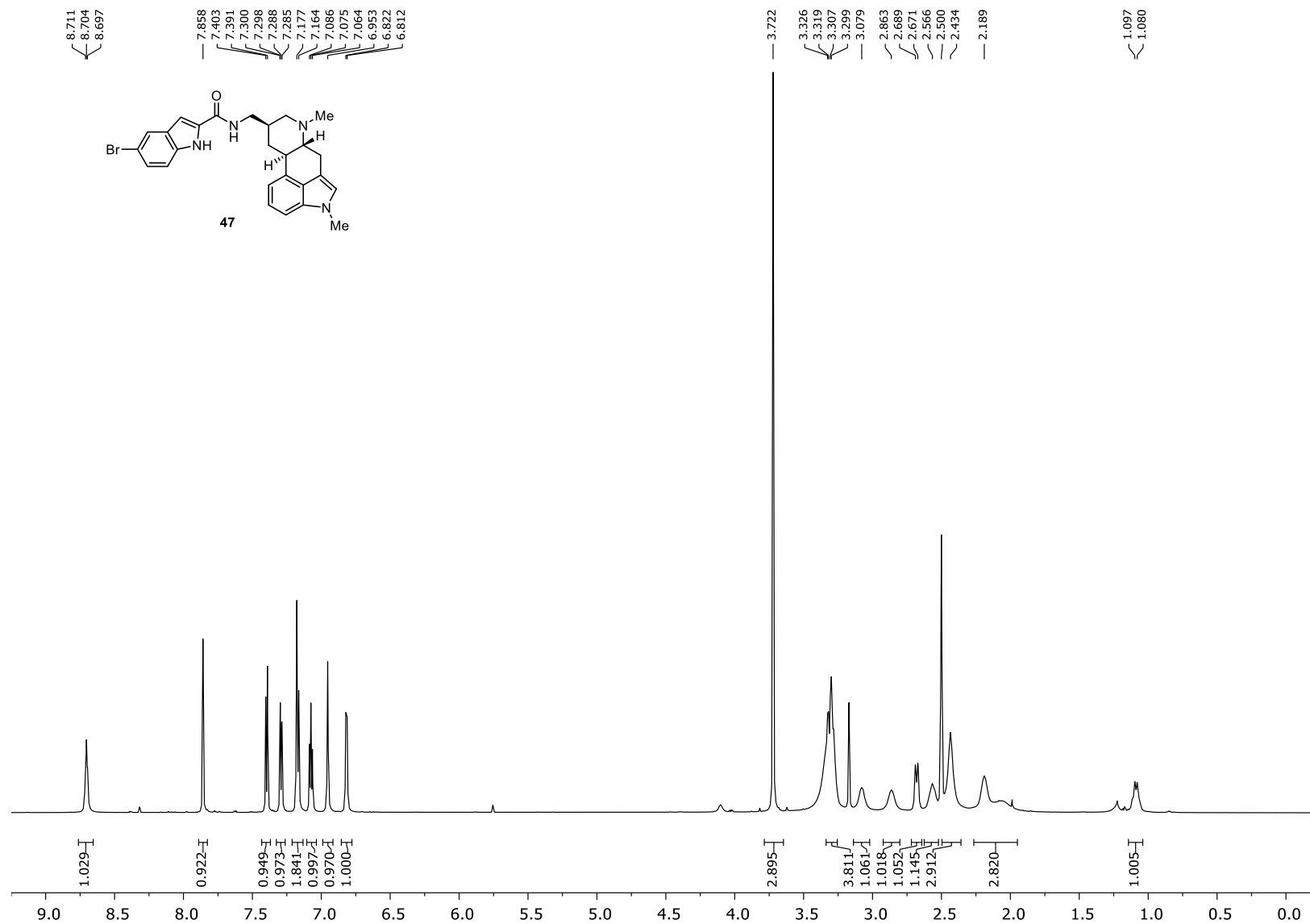
N-2'-Indoloyl ergoline derivative (**46**) (^1H NMR; 700 MHz; CDCl_3)



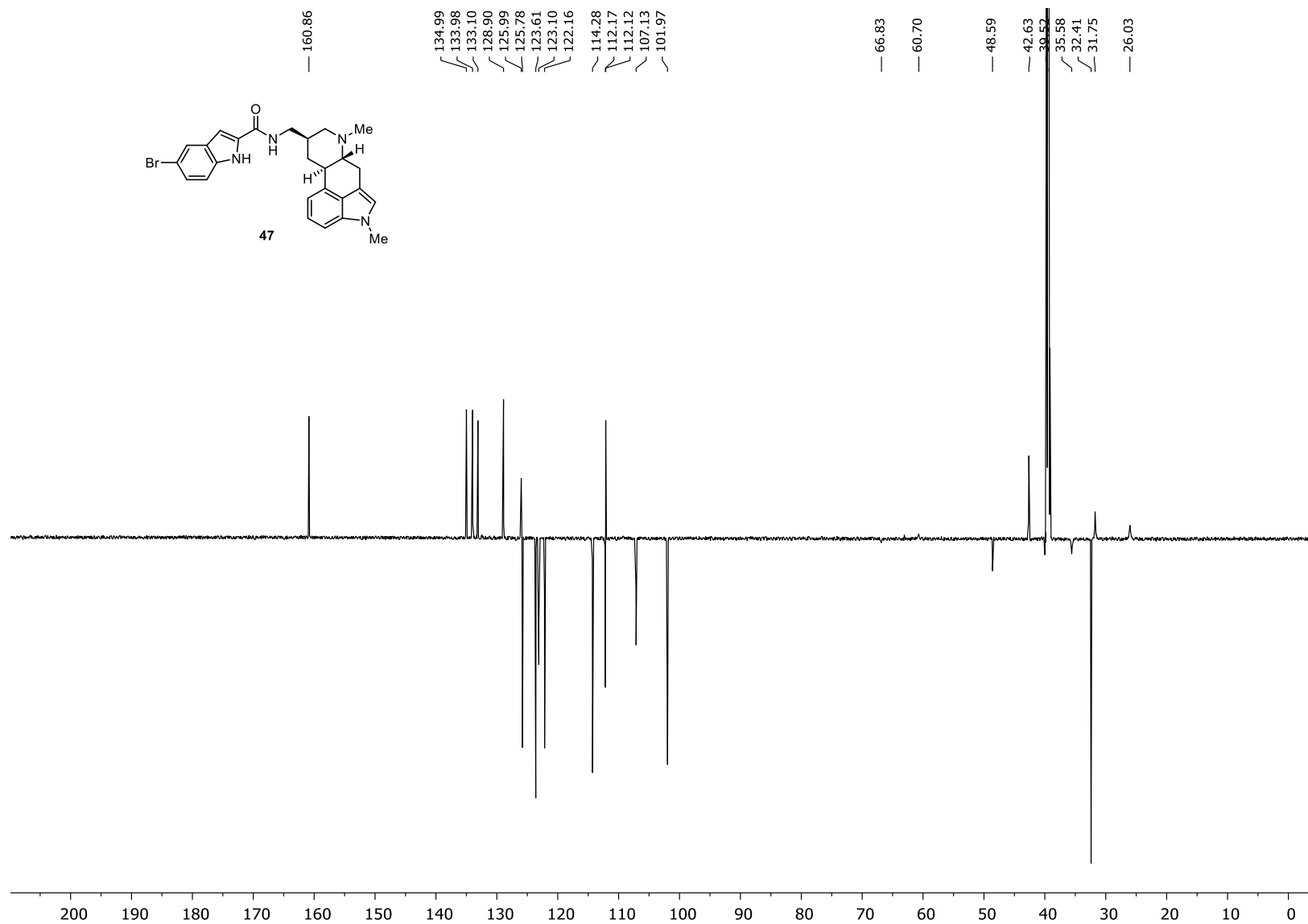
N-2'-Indoloyl ergoline derivative (**46**) (^{13}C NMR; 175 MHz; CDCl_3)



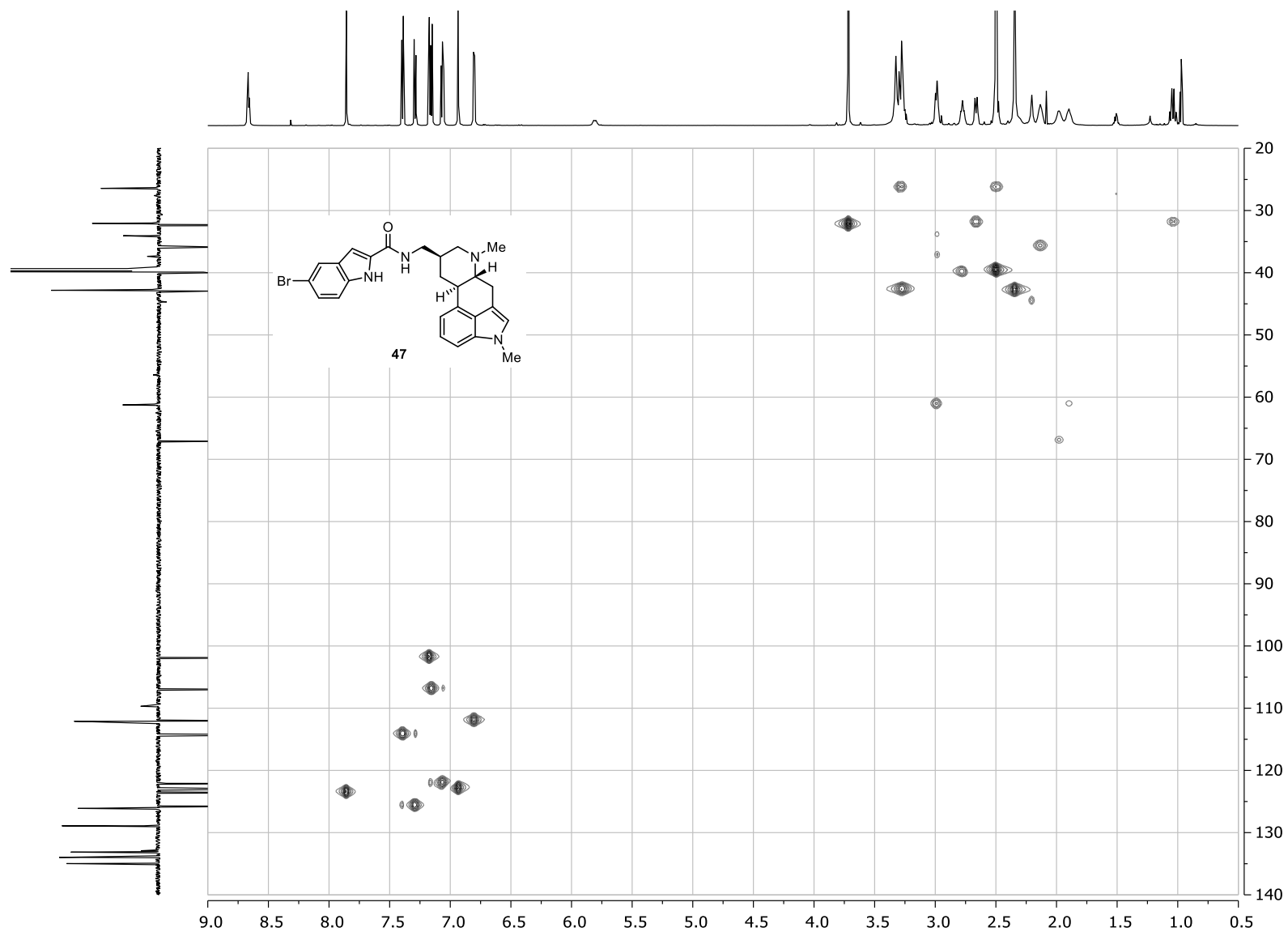
N-(5'-Bromoindol-2'-oyl) ergoline derivative (**47**) (^1H NMR; 700 MHz; $\text{DMSO}-d_6$)



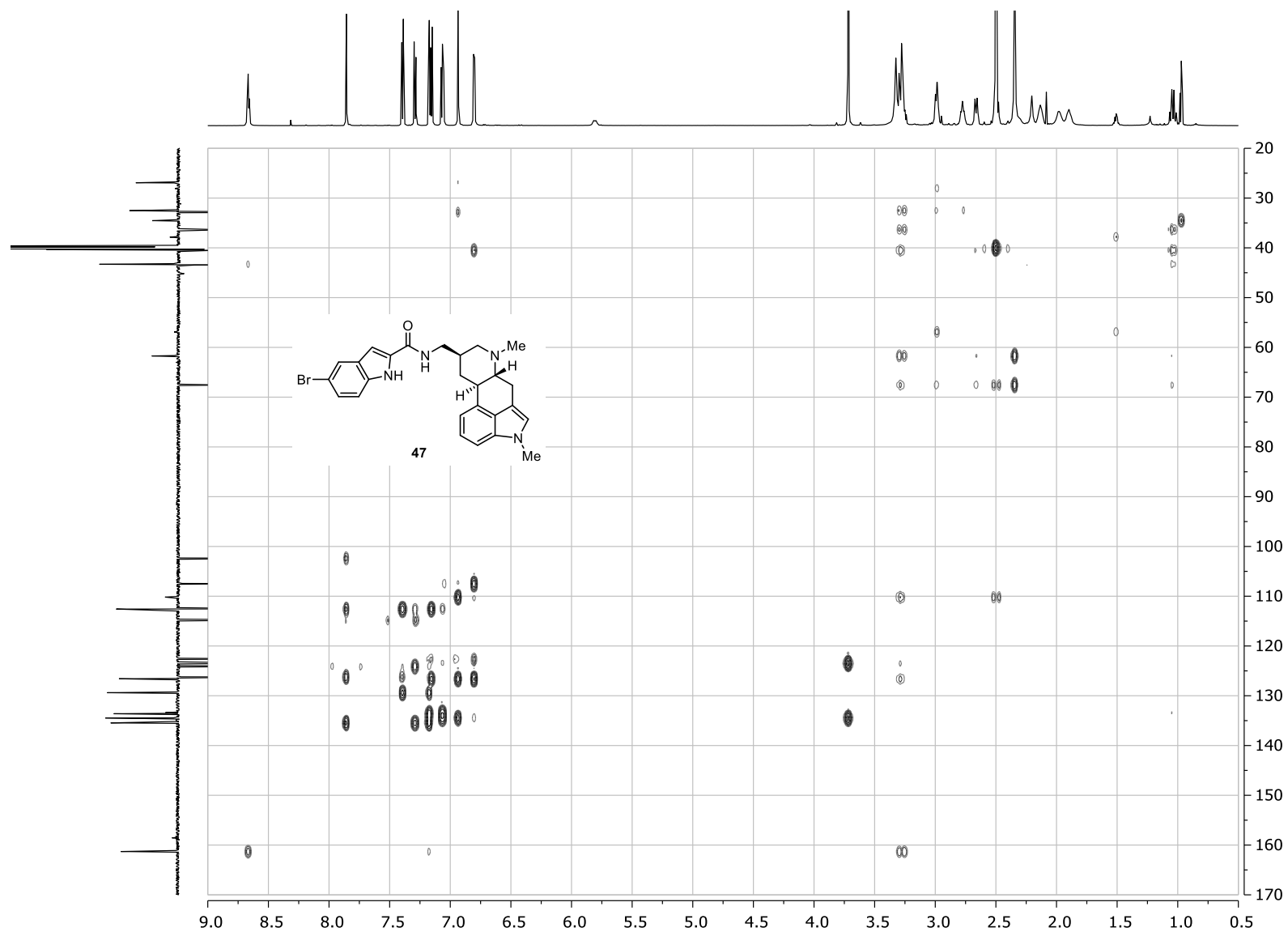
N-(5'-Bromoindol-2'-oyl) ergoline derivative (**47**) (^{13}C NMR; 175 MHz; $\text{DMSO-}d_6$)



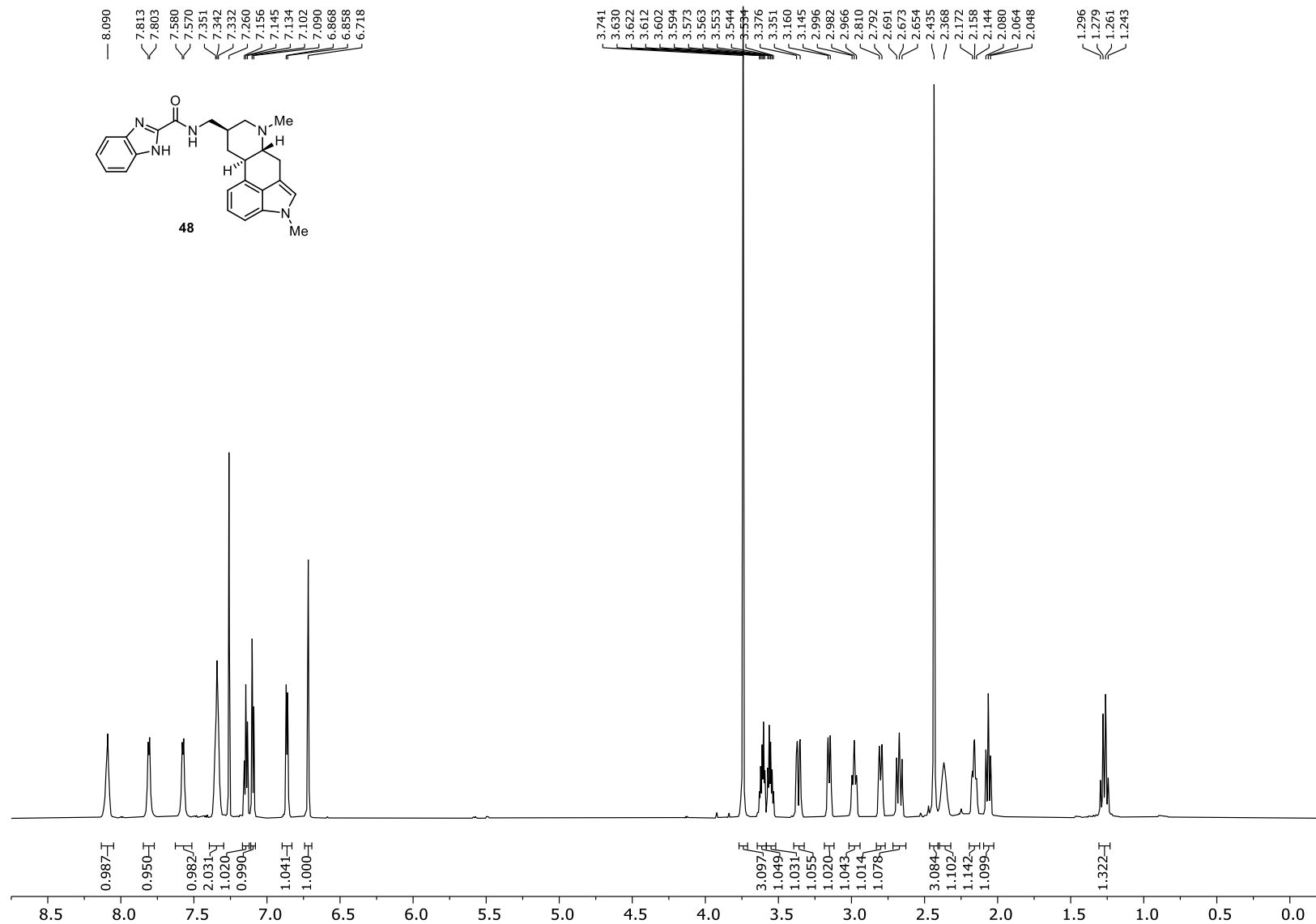
N-(5'-Bromoindol-2'-oyl) ergoline derivative (**47**) (HSQC; DMSO-*d*₆)



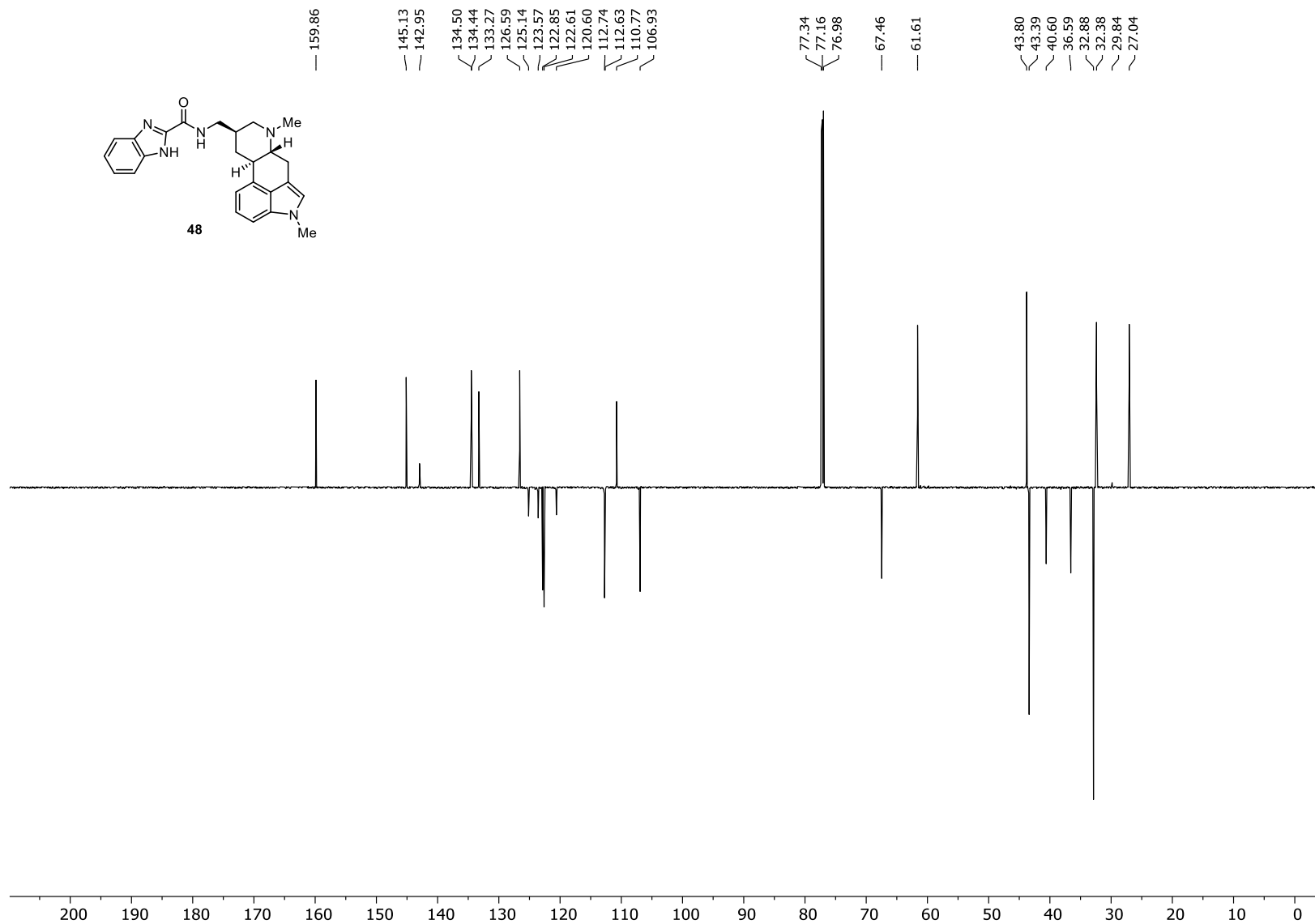
N-(5'-Bromoindol-2'-oyl) ergoline derivative (**47**) (HMBC; DMSO-*d*₆)



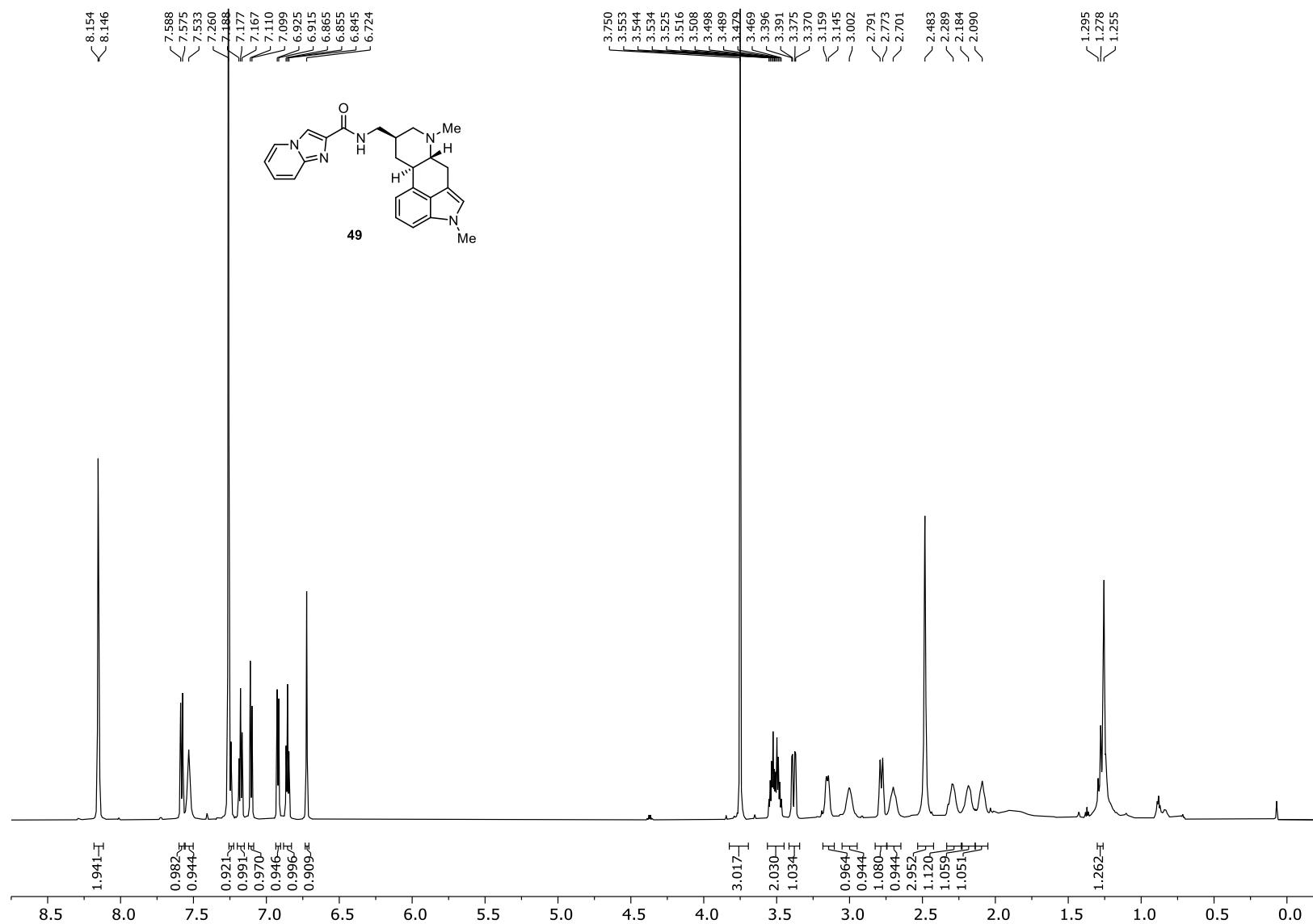
N-(2'-Benzimidazolyl) ergoline derivative (**48**) (^1H NMR; 700 MHz; CDCl_3)



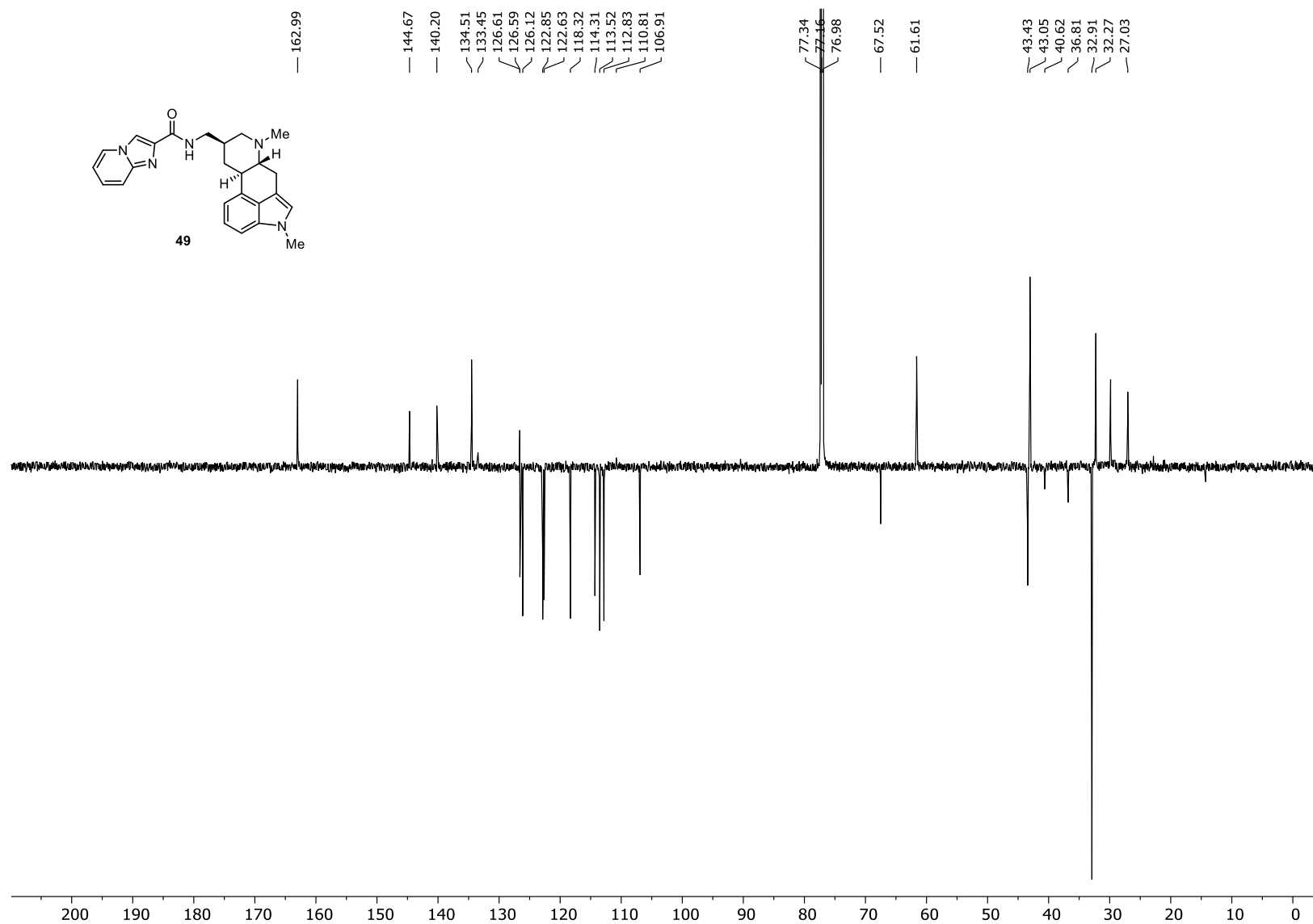
N-(2'-Benzimidazolyl) ergoline derivative (**48**) (^{13}C NMR; 175 MHz; CDCl_3)



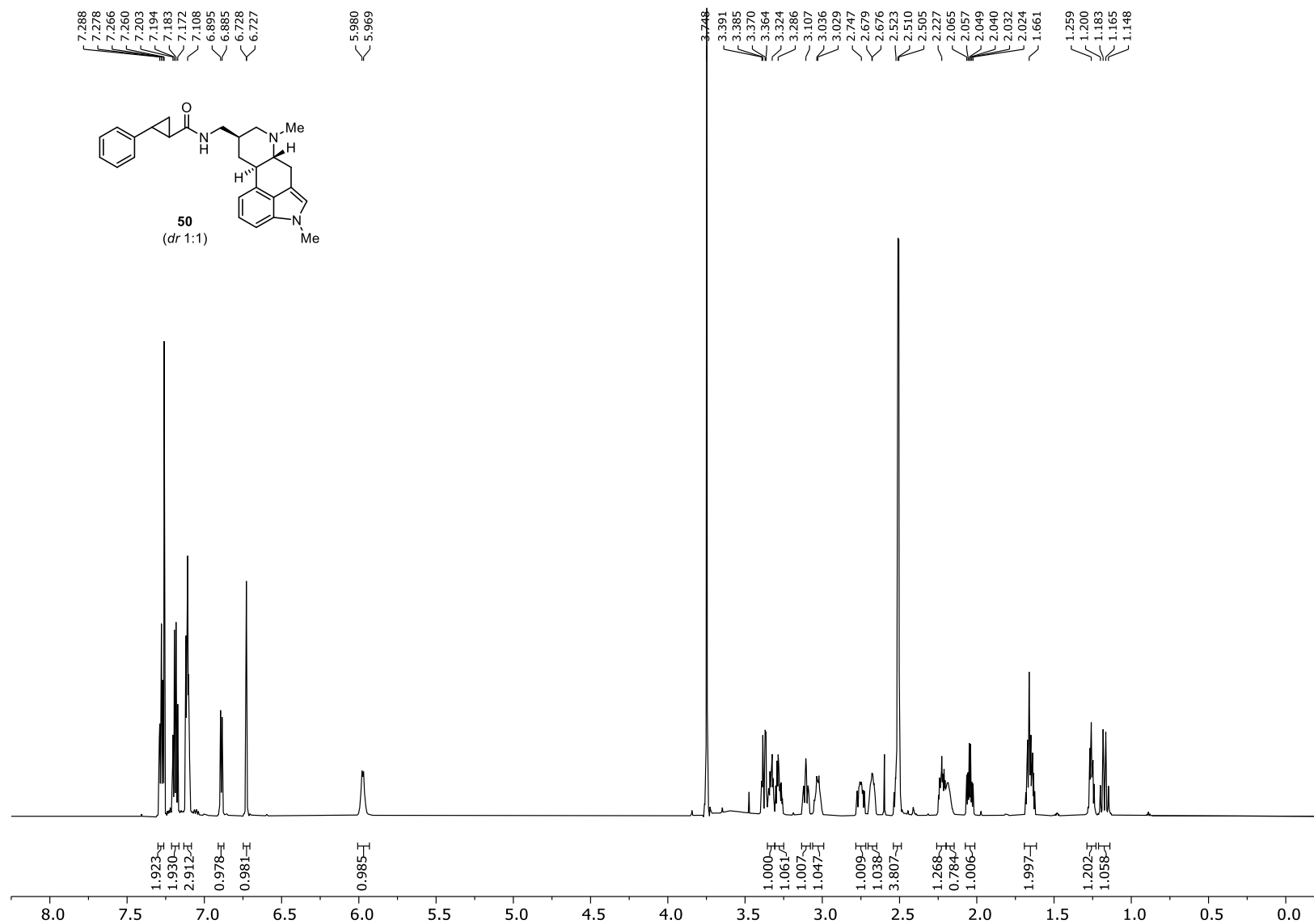
N-(Imidazo[1,2-*a*]pyridine-2'-oyl) ergoline derivative (**49**) (^1H NMR; 700 MHz; CDCl_3)



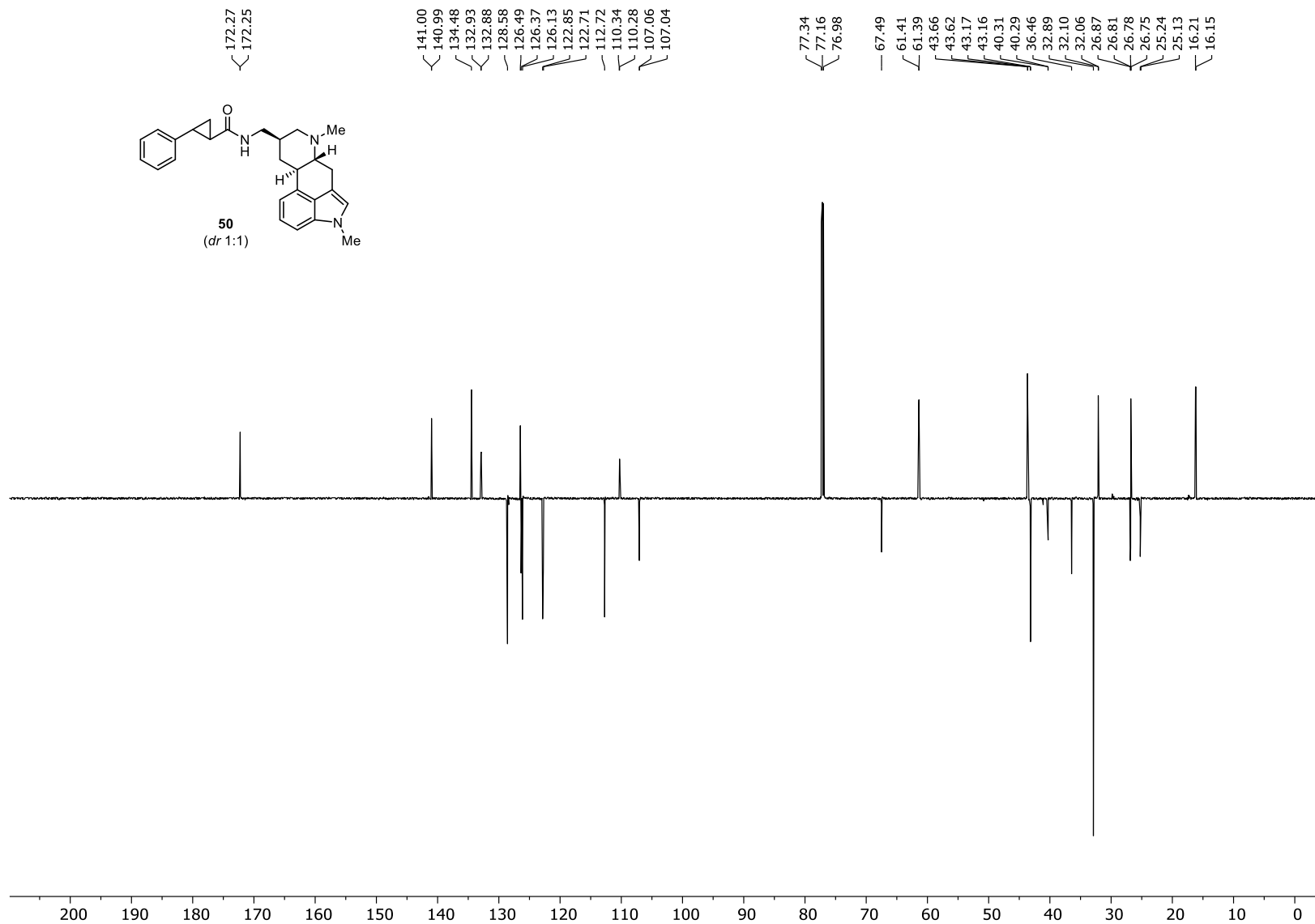
N-(Imidazo[1,2-*a*]pyridine-2'-oyl) ergoline derivative (**49**) (^{13}C NMR; 175 MHz; CDCl_3)



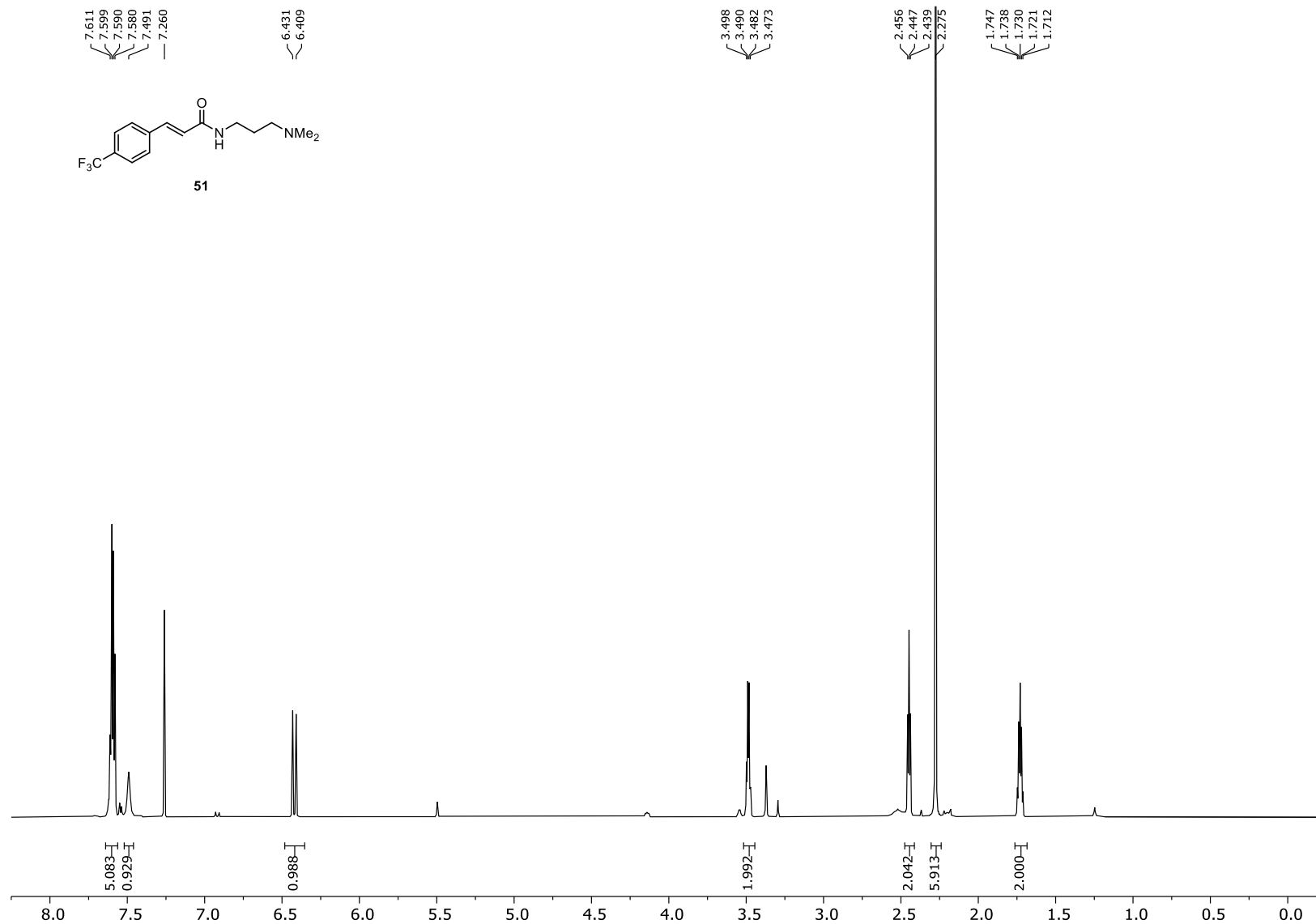
N^1,N^6 -Dimethylergoline 2'-phenylcyclopropane-1'-carboxamide (**50**) (^1H NMR; 700 MHz; CDCl_3)



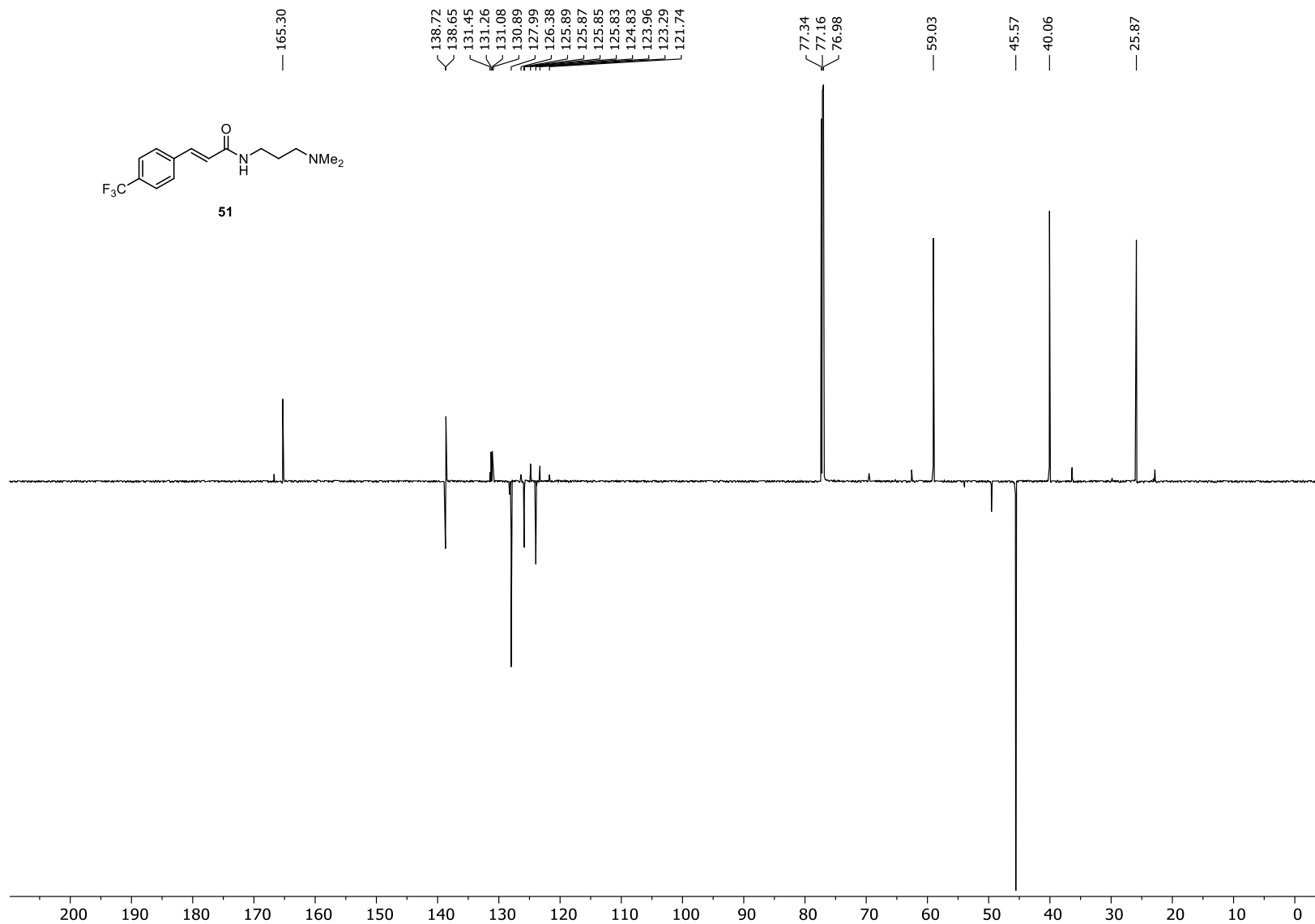
*N*¹,*N*⁶-Dimethylergoline 2'-phenylcyclopropane-1'-carboxamide (**50**) (¹³C NMR; 175 MHz; CDCl₃)



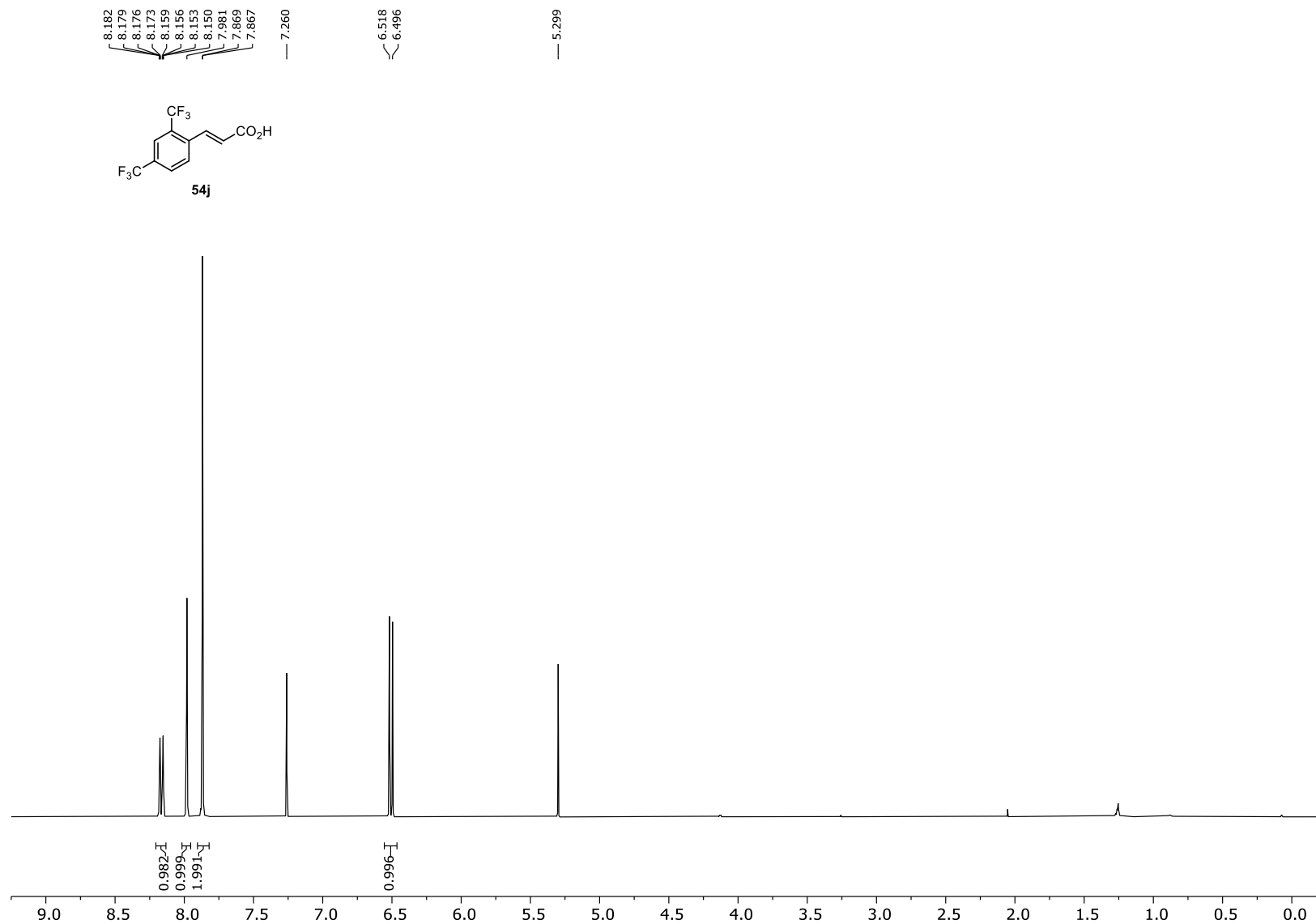
(*E*)-*N*-(3-(Dimethylamino)propyl)-3-(4-trifluoromethylphenyl)acrylamide (**51**) (^1H NMR; 700 MHz; CDCl_3)



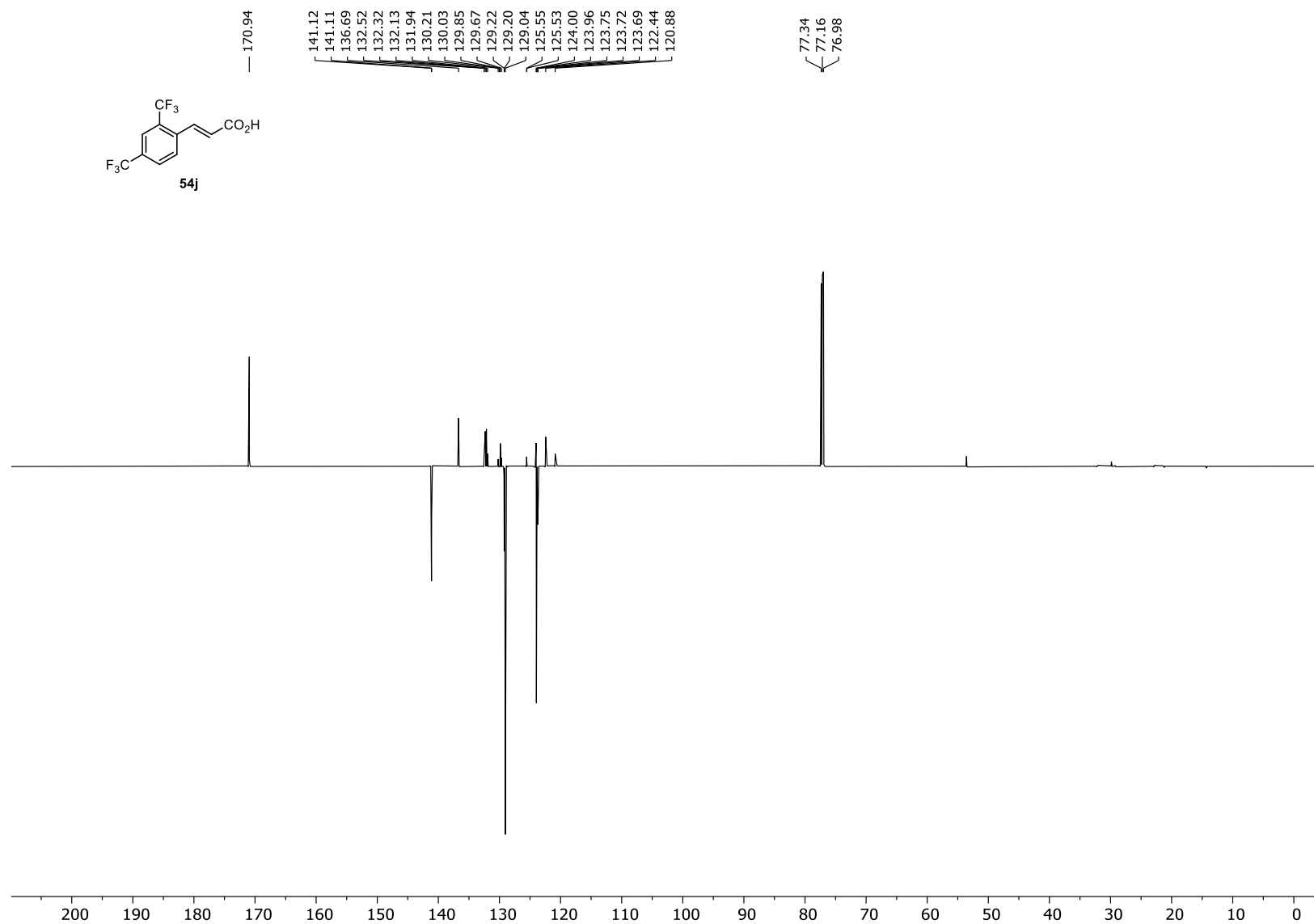
(*E*)-*N*-(3-(Dimethylamino)propyl)-3-(4-trifluoromethylphenyl)acrylamide (**51**) (^{13}C NMR; 175 MHz; CDCl_3)



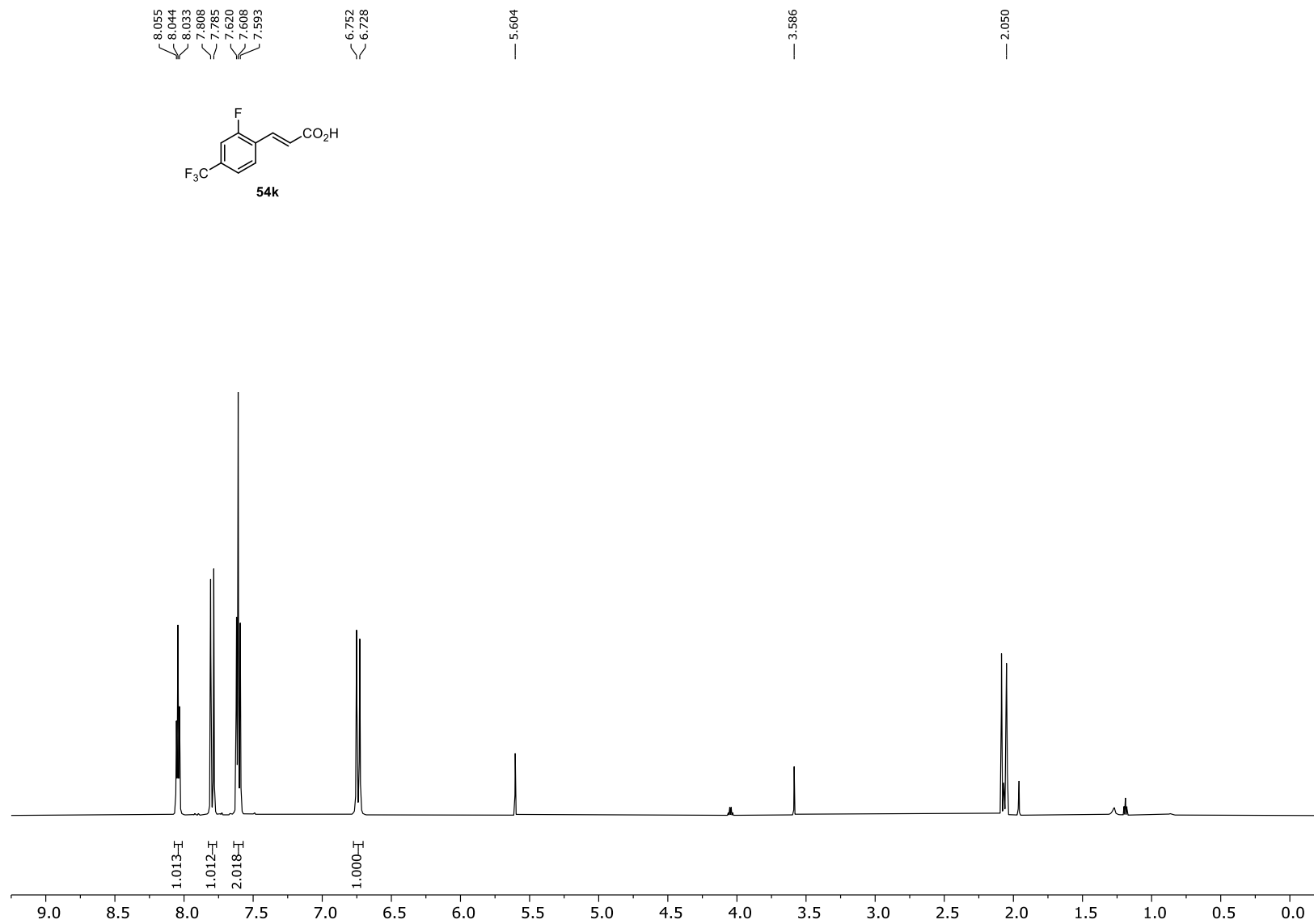
(*E*)-2,4-Di(trifluoromethyl)cinnamic acid (**54j**) (^1H NMR; 700 MHz; CDCl_3)



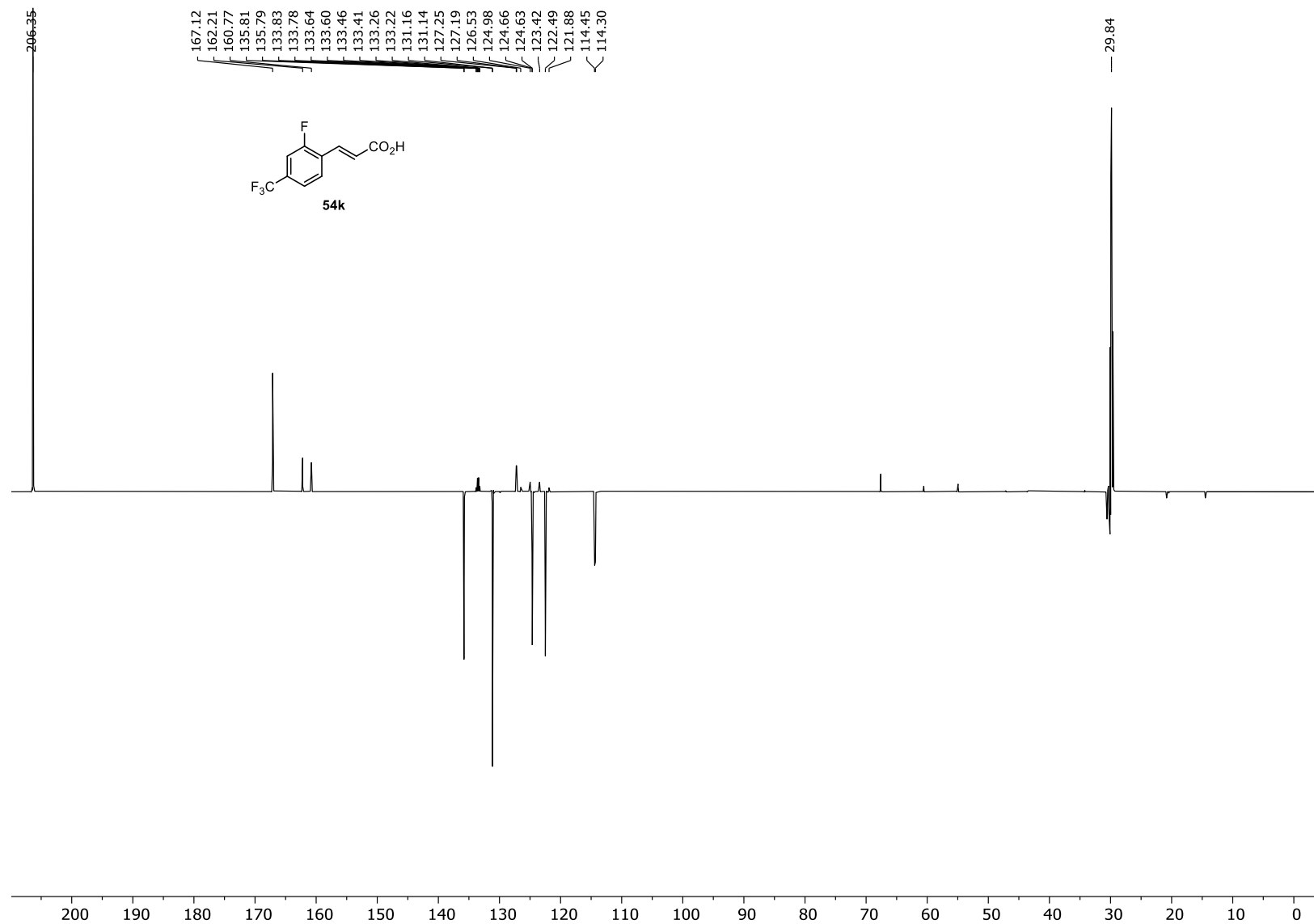
(*E*)-2,4-Di(trifluoromethyl)cinnamic acid (**54j**) (^{13}C NMR; 175 MHz; CDCl_3)



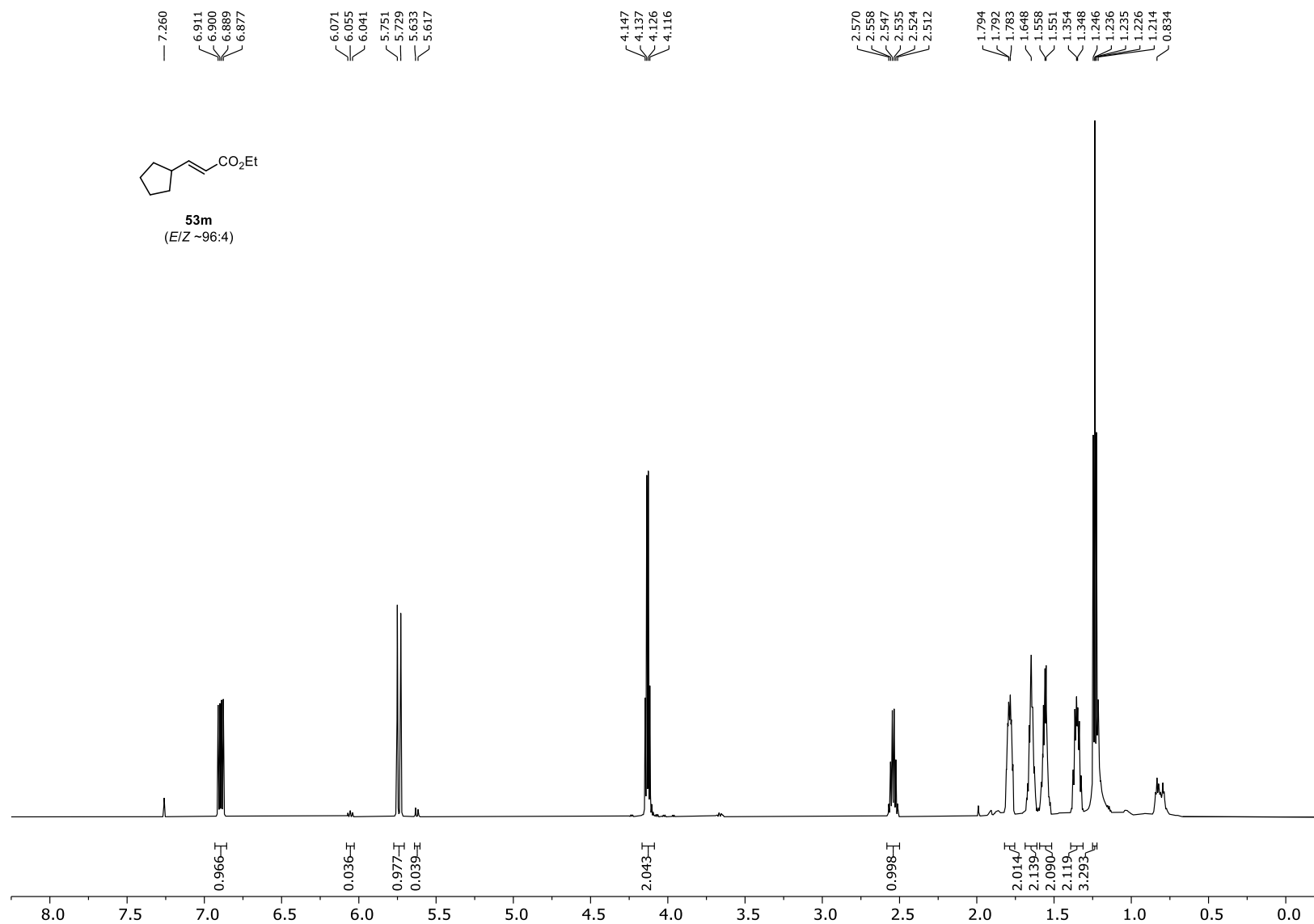
(*E*)-2-Fluoro-4-trifluoromethylcinnamic acid (**54k**) (^1H NMR; 700 MHz; acetone- d_6)



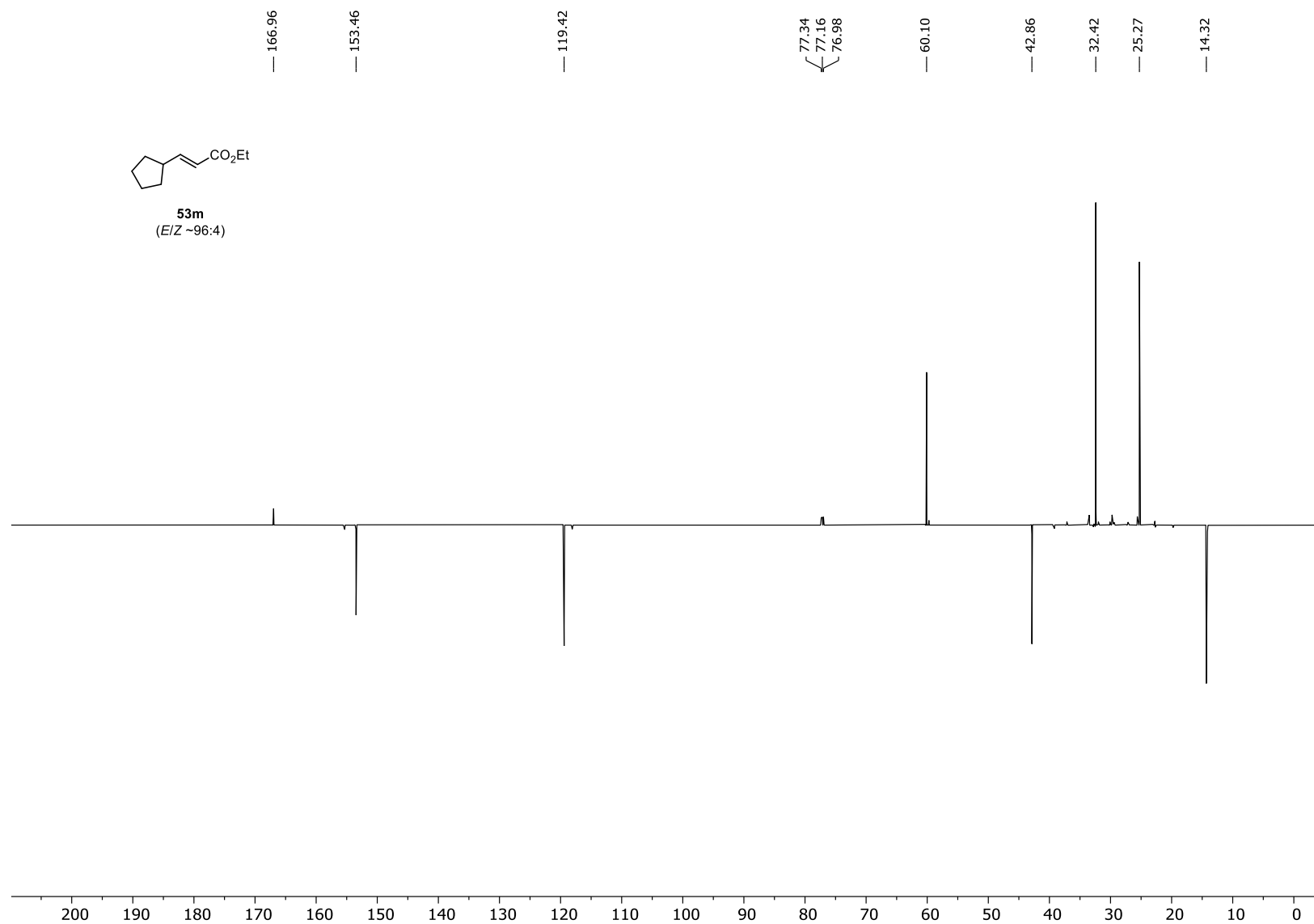
(*E*)-2-Fluoro-4-trifluoromethylcinnamic acid (**54k**) (^{13}C NMR; 175 MHz; acetone- d_6)



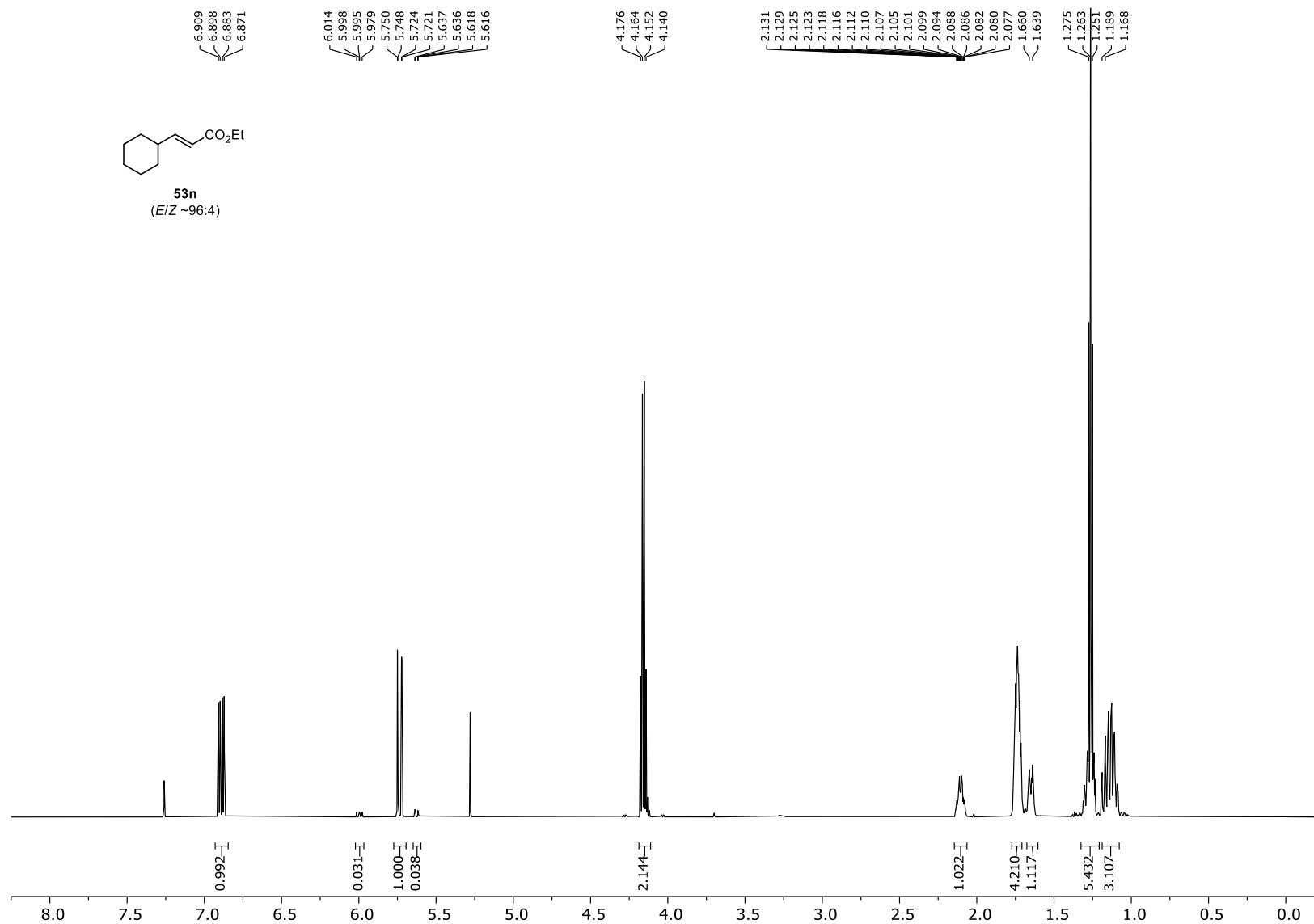
Ethyl (*E*)-3-cyclopentylacrylate (**53m**) (^1H NMR; 700 MHz; CDCl_3)



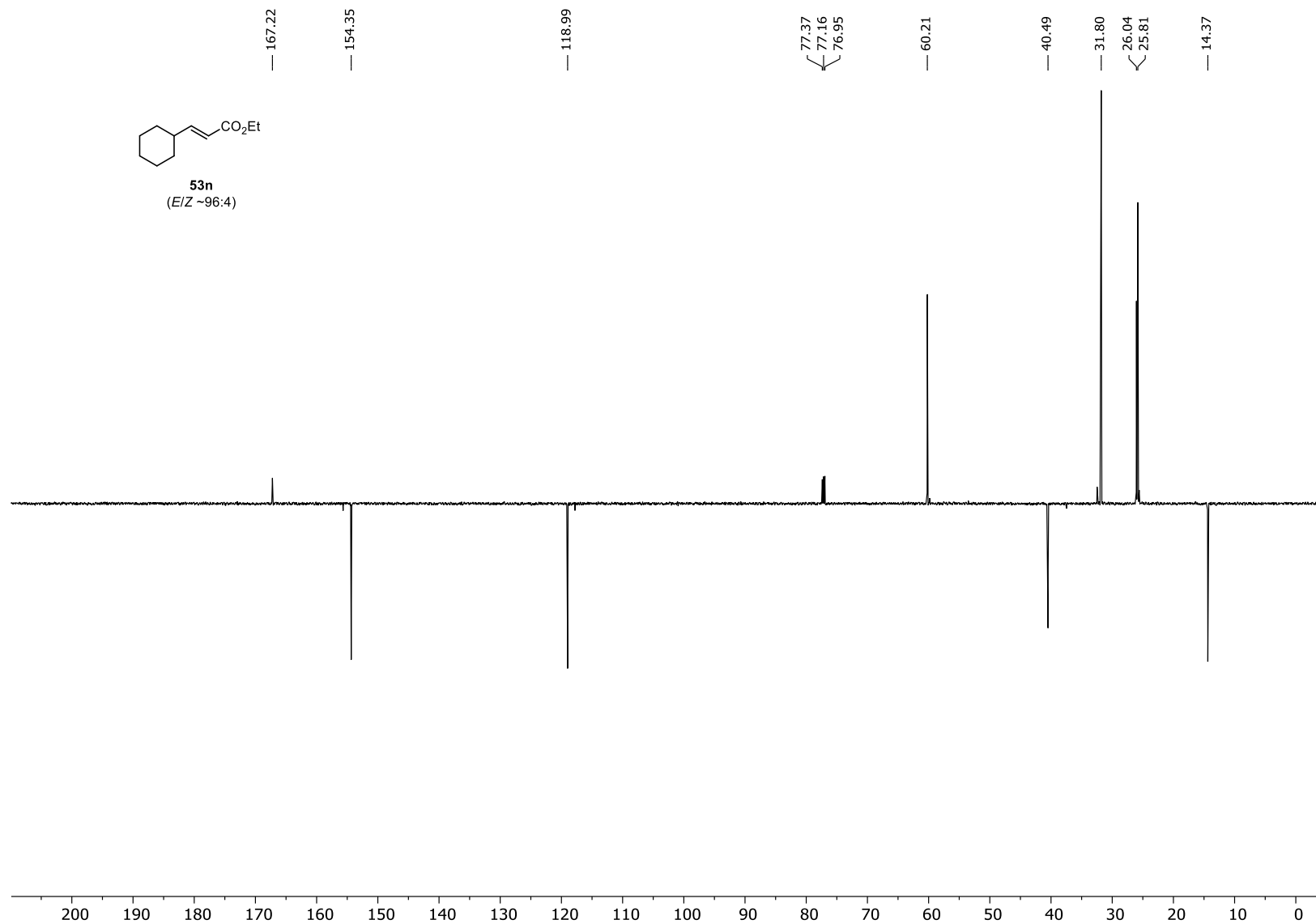
Ethyl (*E*)-3-cyclopentylacrylate (**53m**) (^{13}C NMR; 175 MHz; CDCl_3)



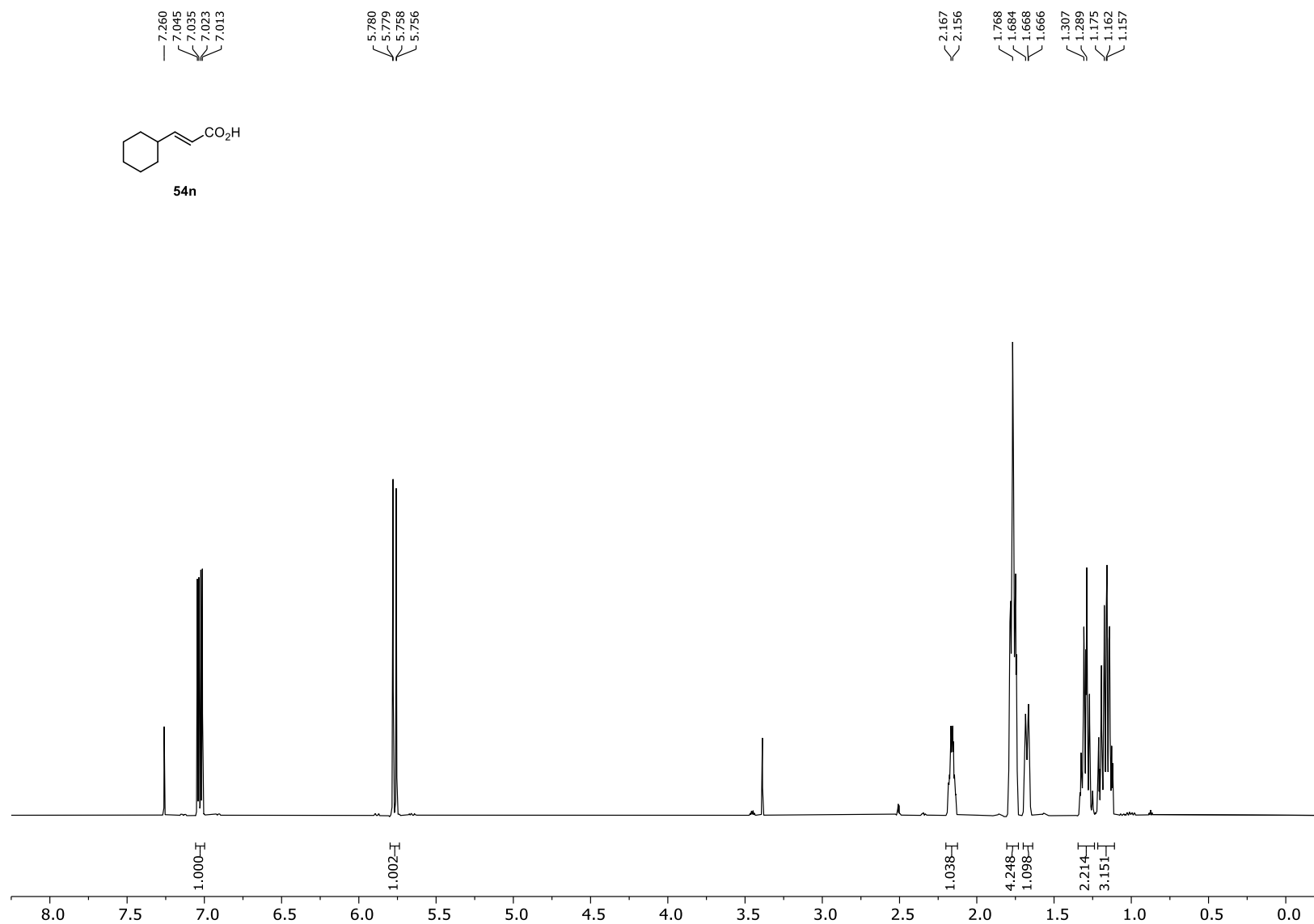
Ethyl (*E*)-3-cyclohexylacrylate (**53n**) (^1H NMR; 700 MHz; CDCl_3)



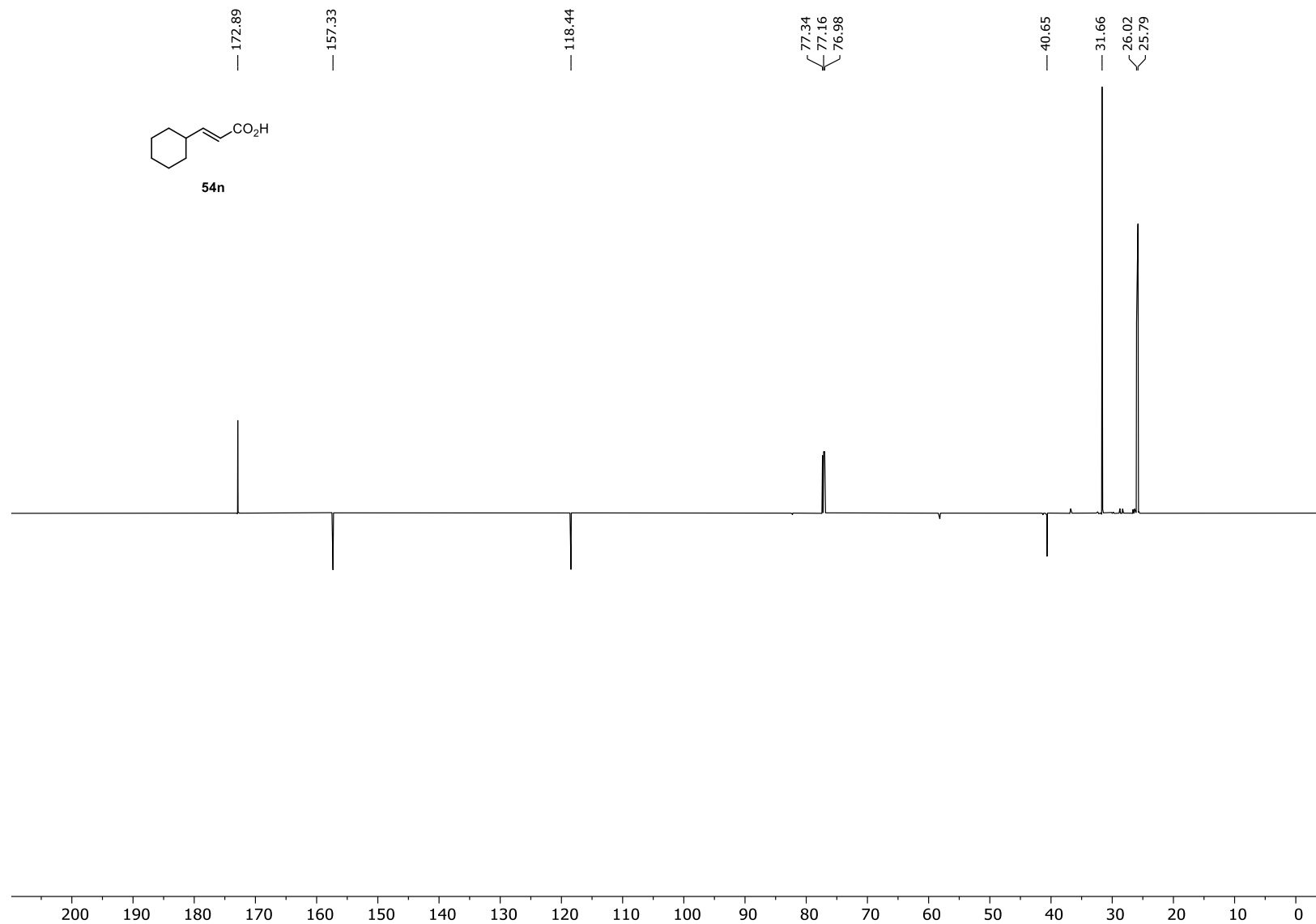
Ethyl (*E*)-3-cyclohexylacrylate (**53n**) (^{13}C NMR; 175 MHz; CDCl_3)



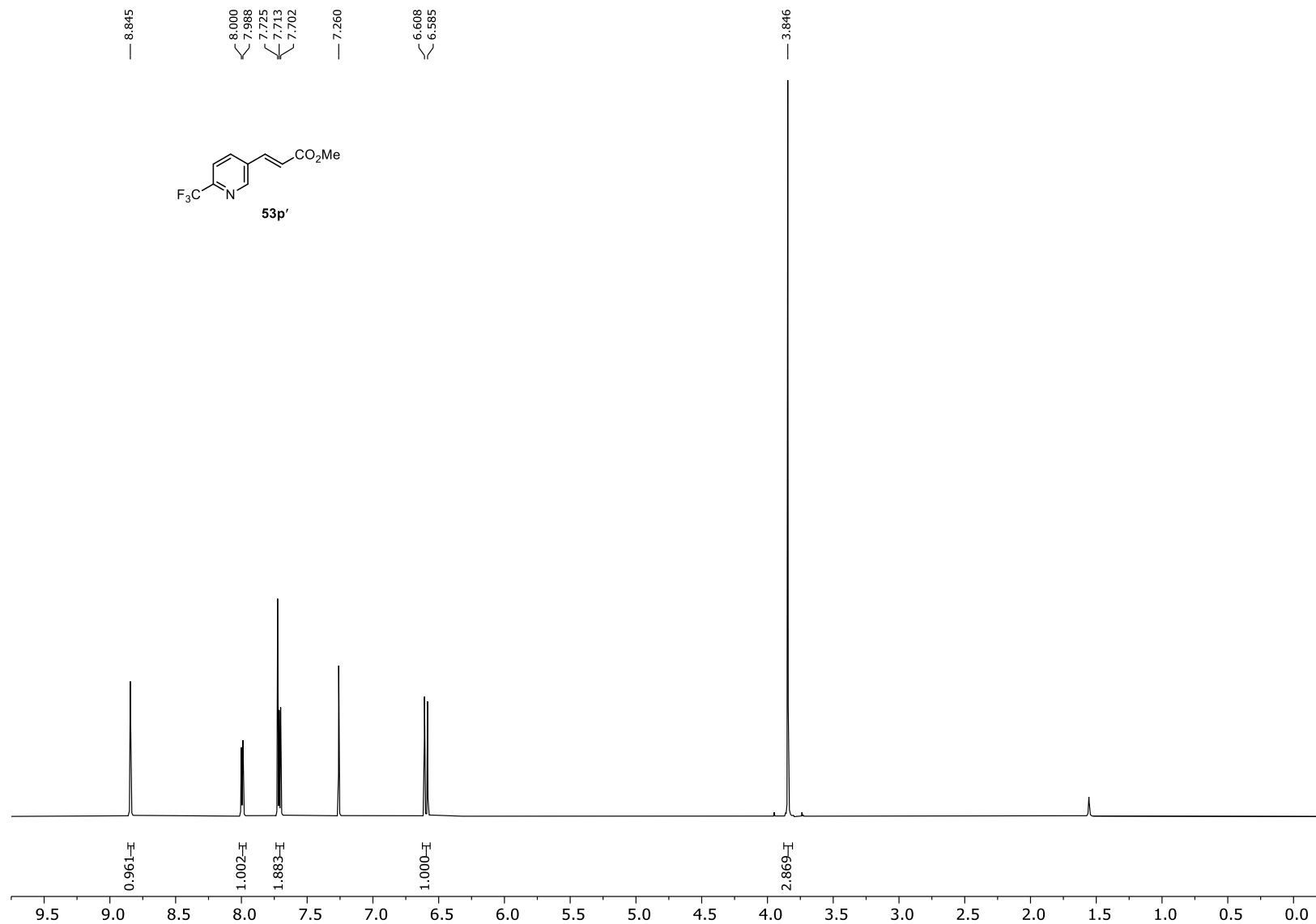
(*E*)-3-Cyclohexylacrylic acid (**54n**) (^1H NMR; 700 MHz; CDCl_3)



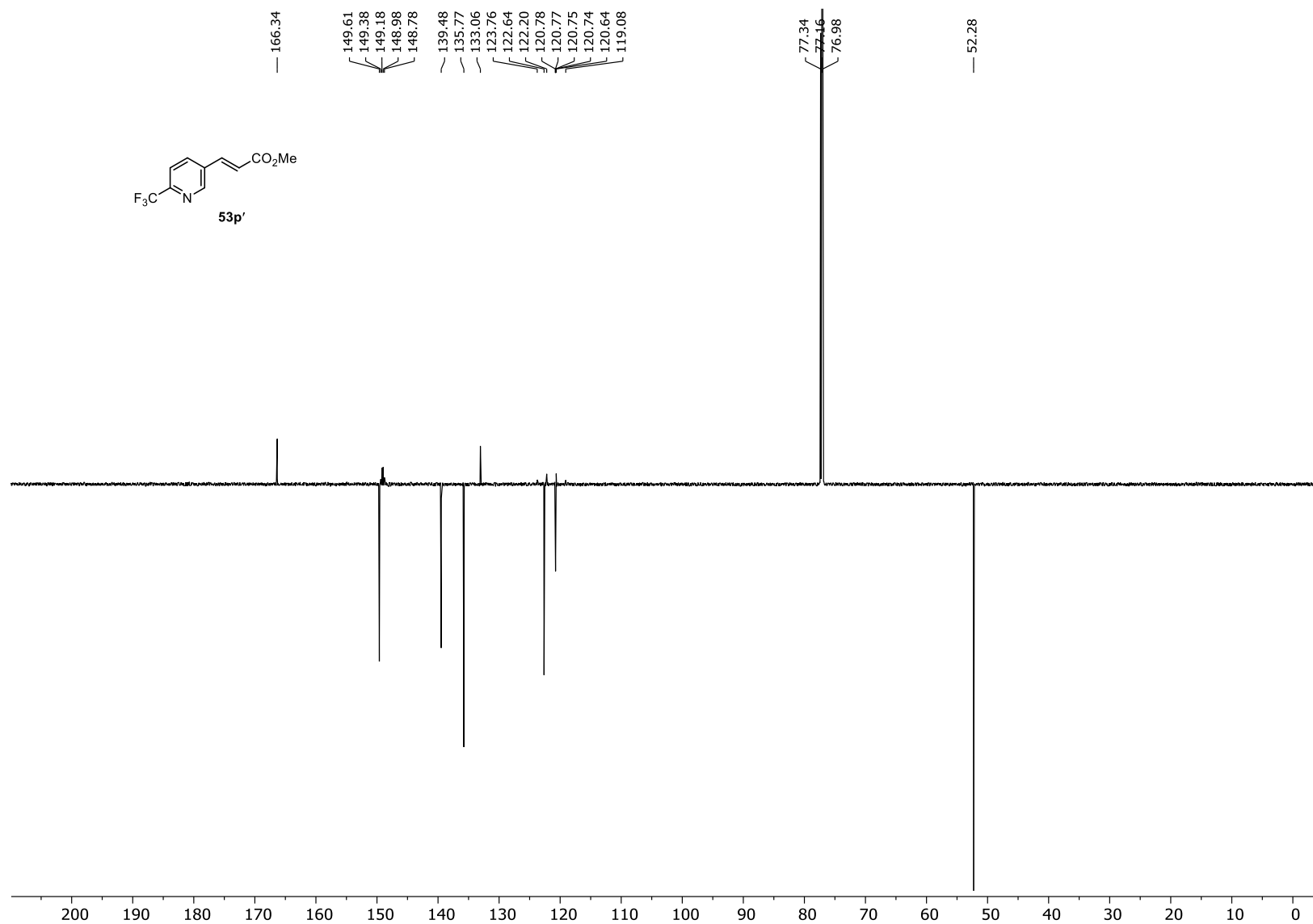
(*E*)-3-Cyclohexylacrylic acid (**54n**) (^{13}C NMR; 175 MHz; CDCl_3)



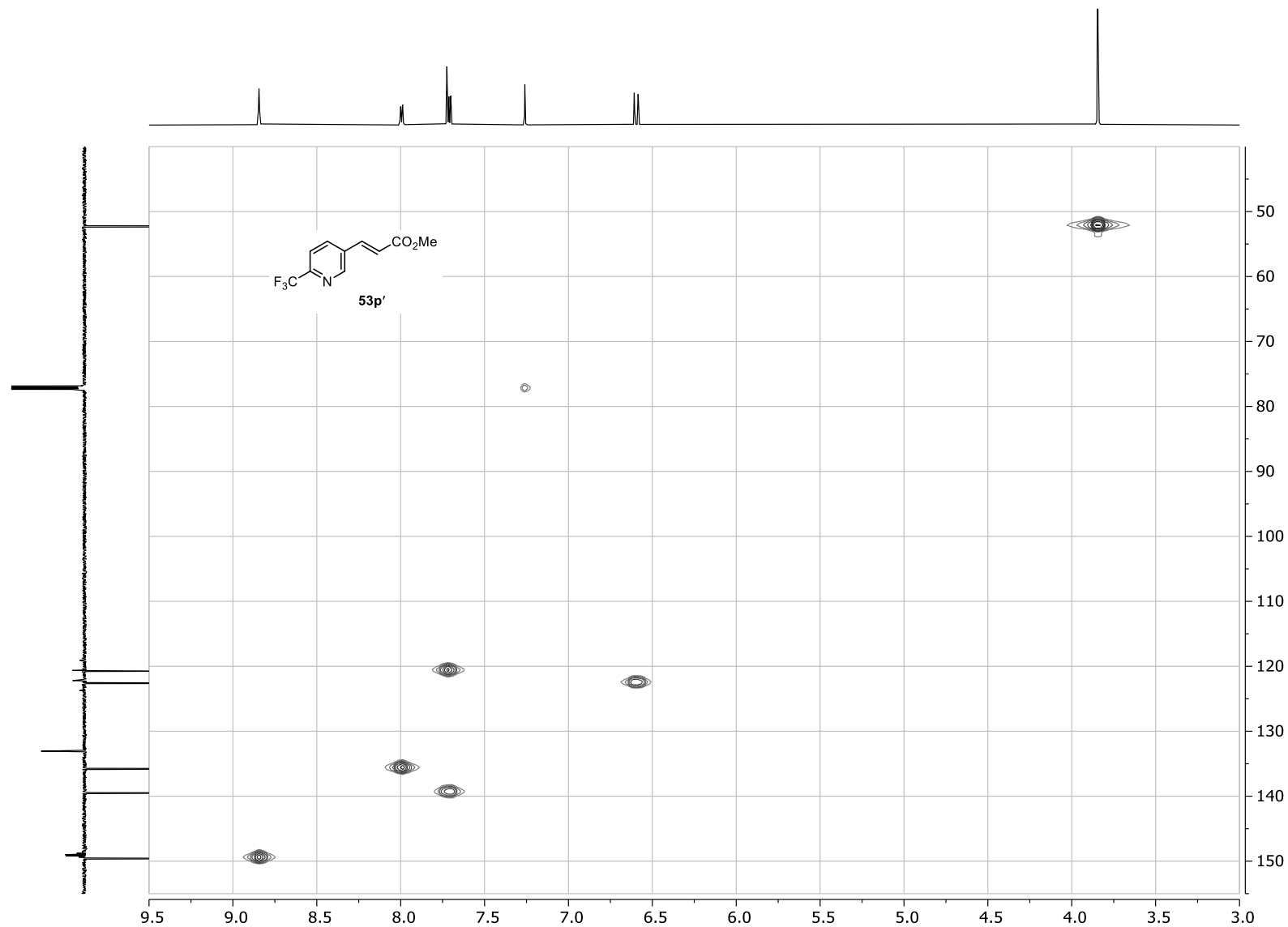
Methyl (*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylate (**53p'**) (^1H NMR; 700 MHz; CDCl_3)



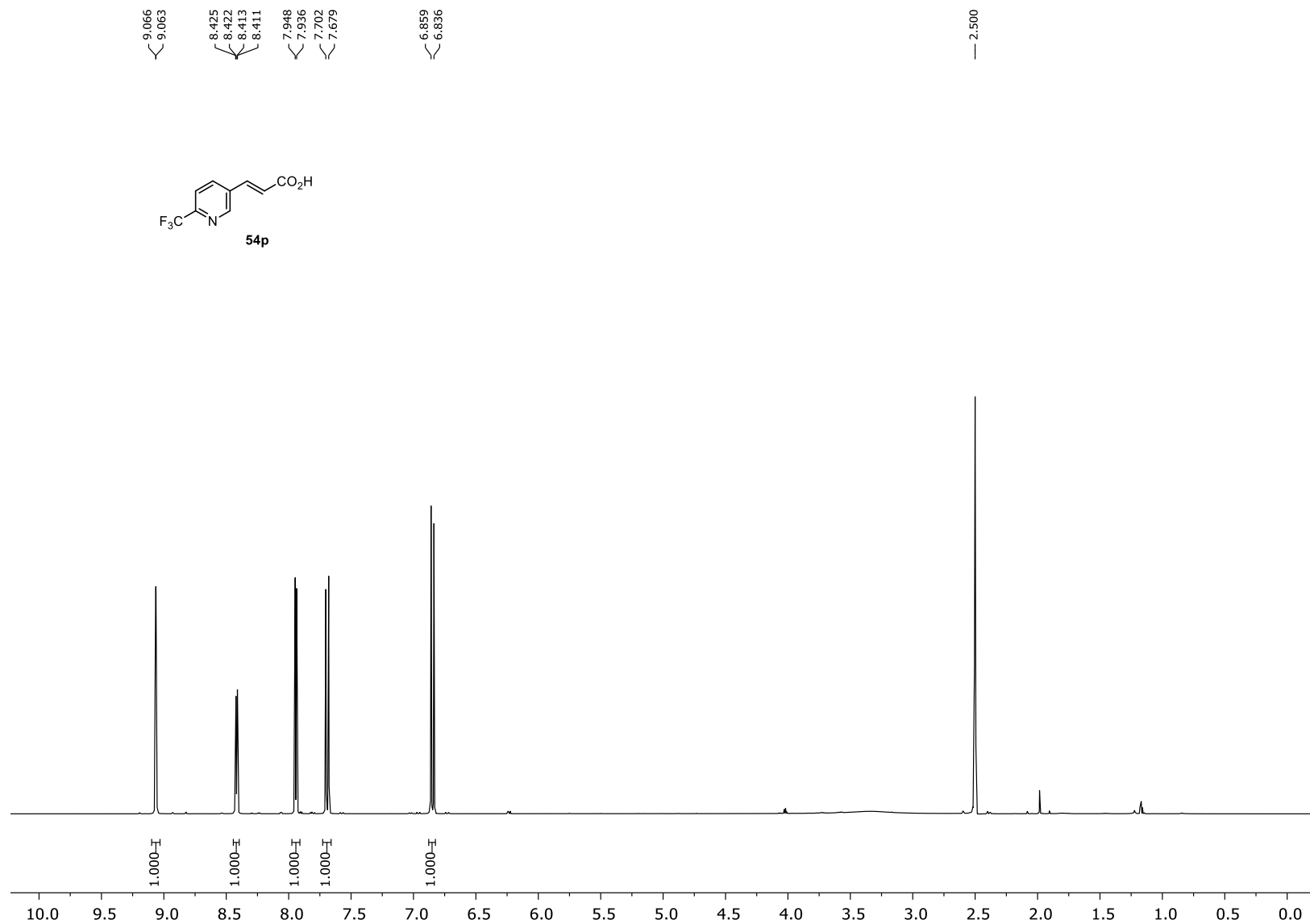
Methyl (*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylate (**53p'**) (^{13}C NMR; 175 MHz; CDCl_3)



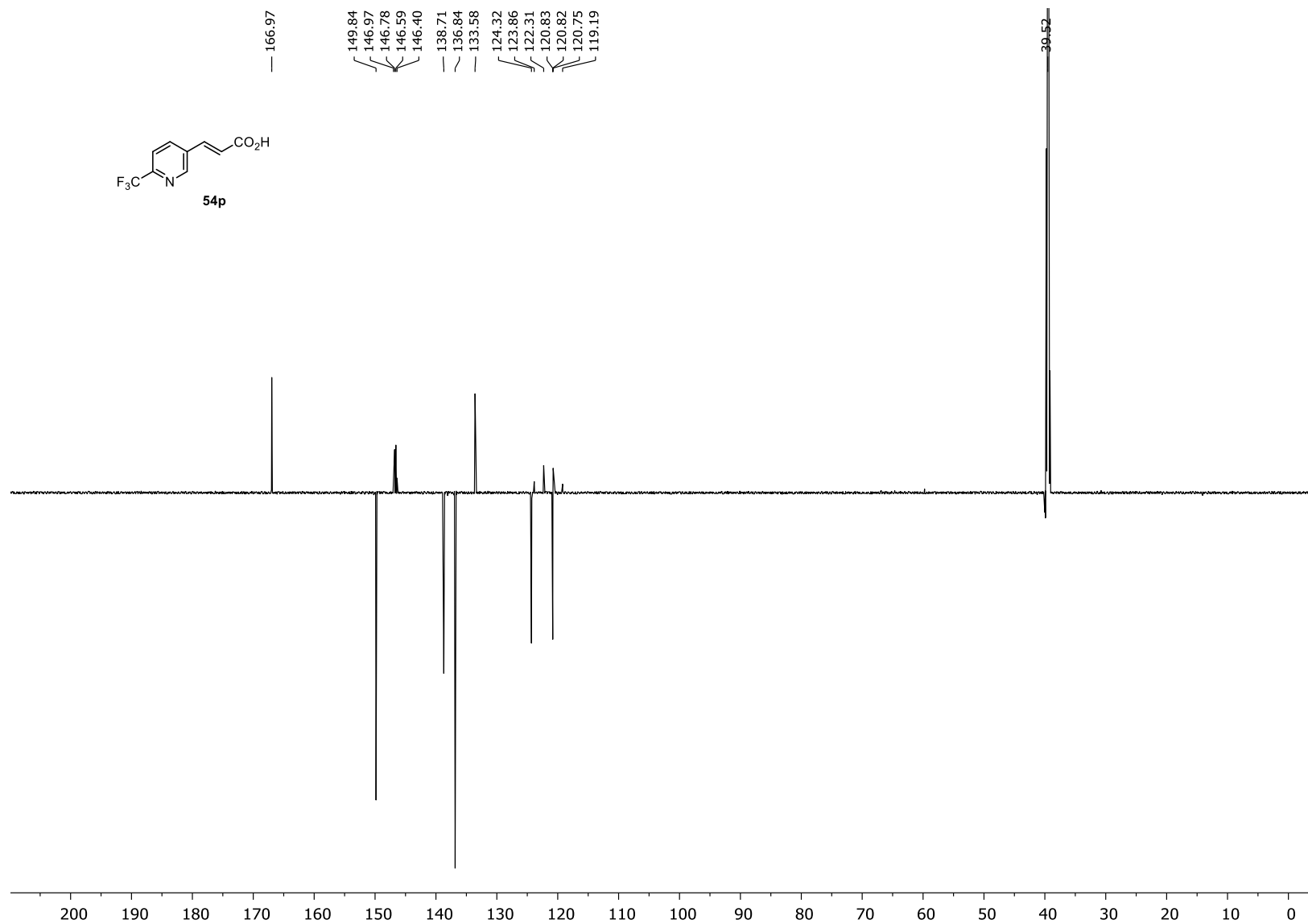
Methyl (*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylate (**53p'**) (HSQC; CDCl₃)



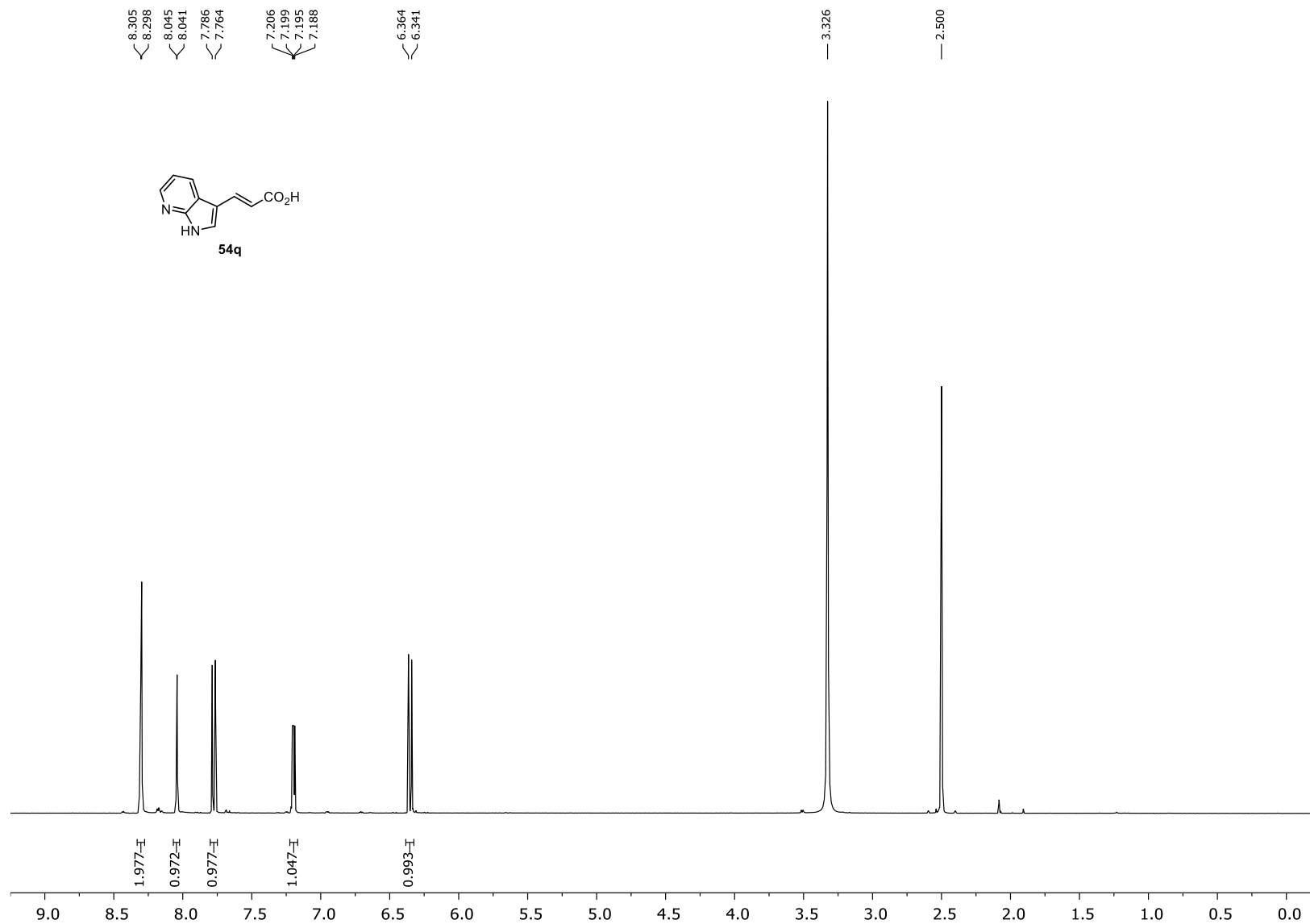
(*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylic acid (**54p**) (^1H NMR; 700 MHz; $\text{DMSO}-d_6$)



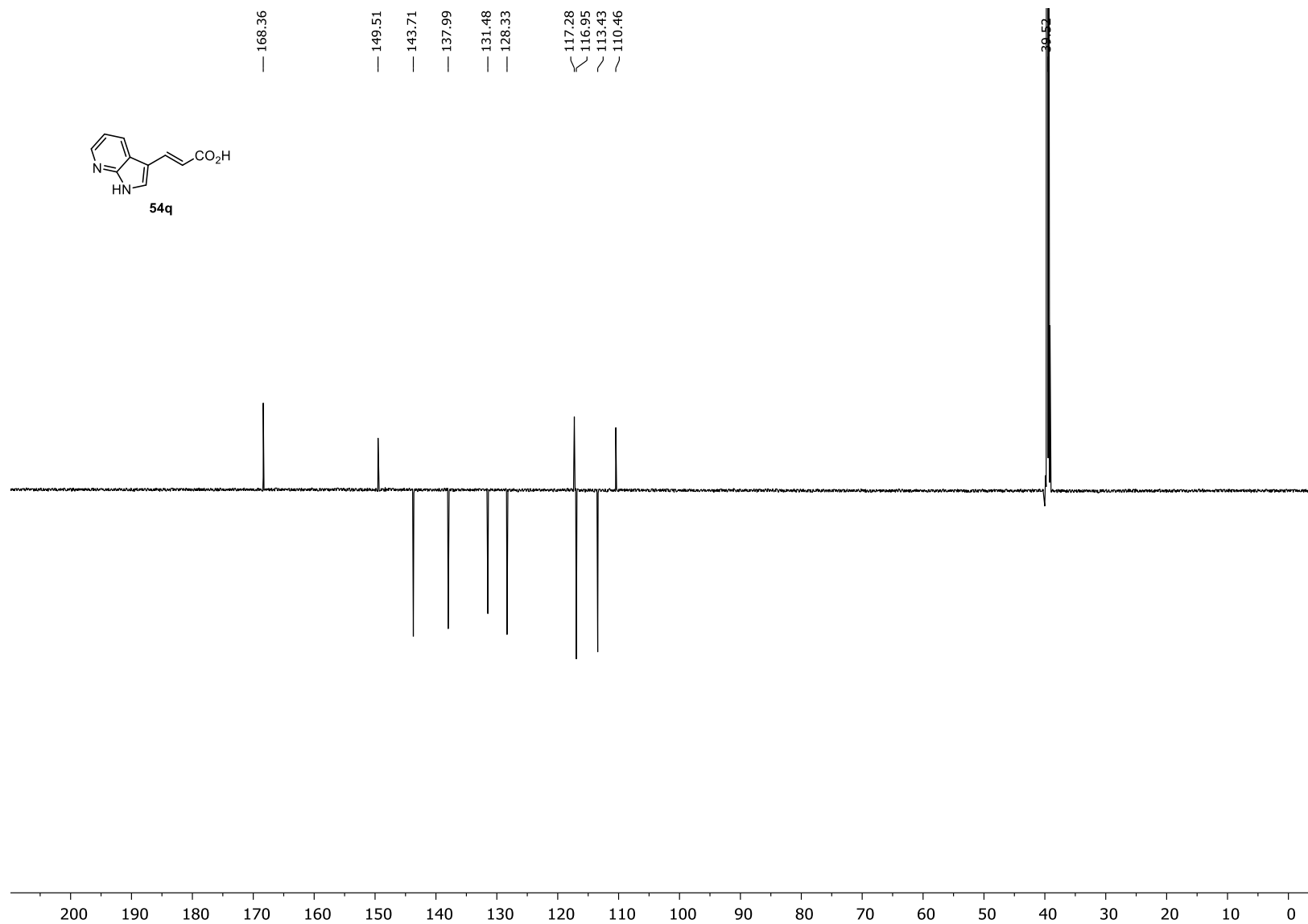
(*E*)-3'-(4-Trifluoromethyl-3-pyridyl)-acrylic acid (**54p**) (^{13}C NMR; 175 MHz; $\text{DMSO-}d_6$)



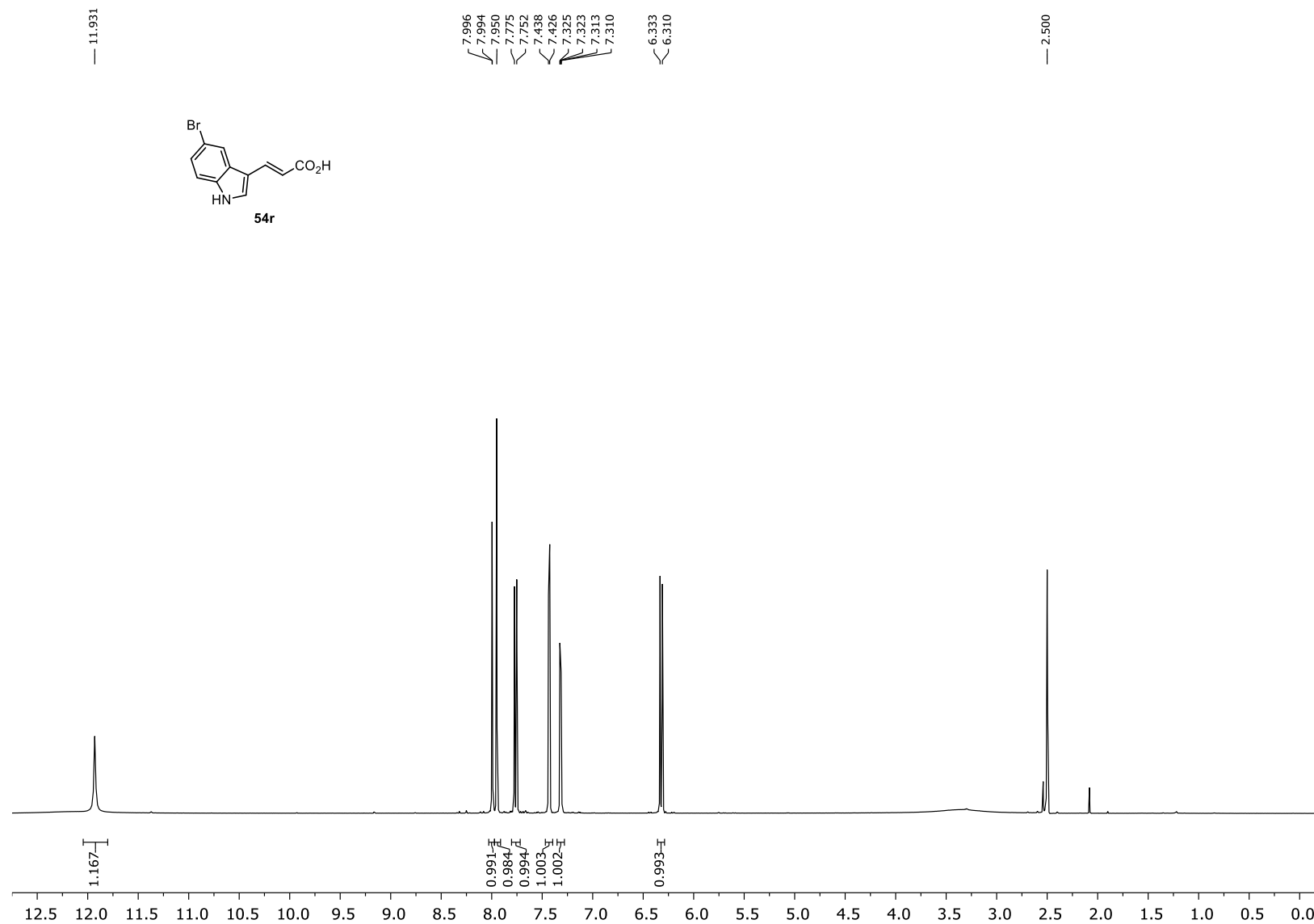
(*E*)-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylic acid (**54q**) (^1H NMR; 700 MHz; DMSO- d_6)



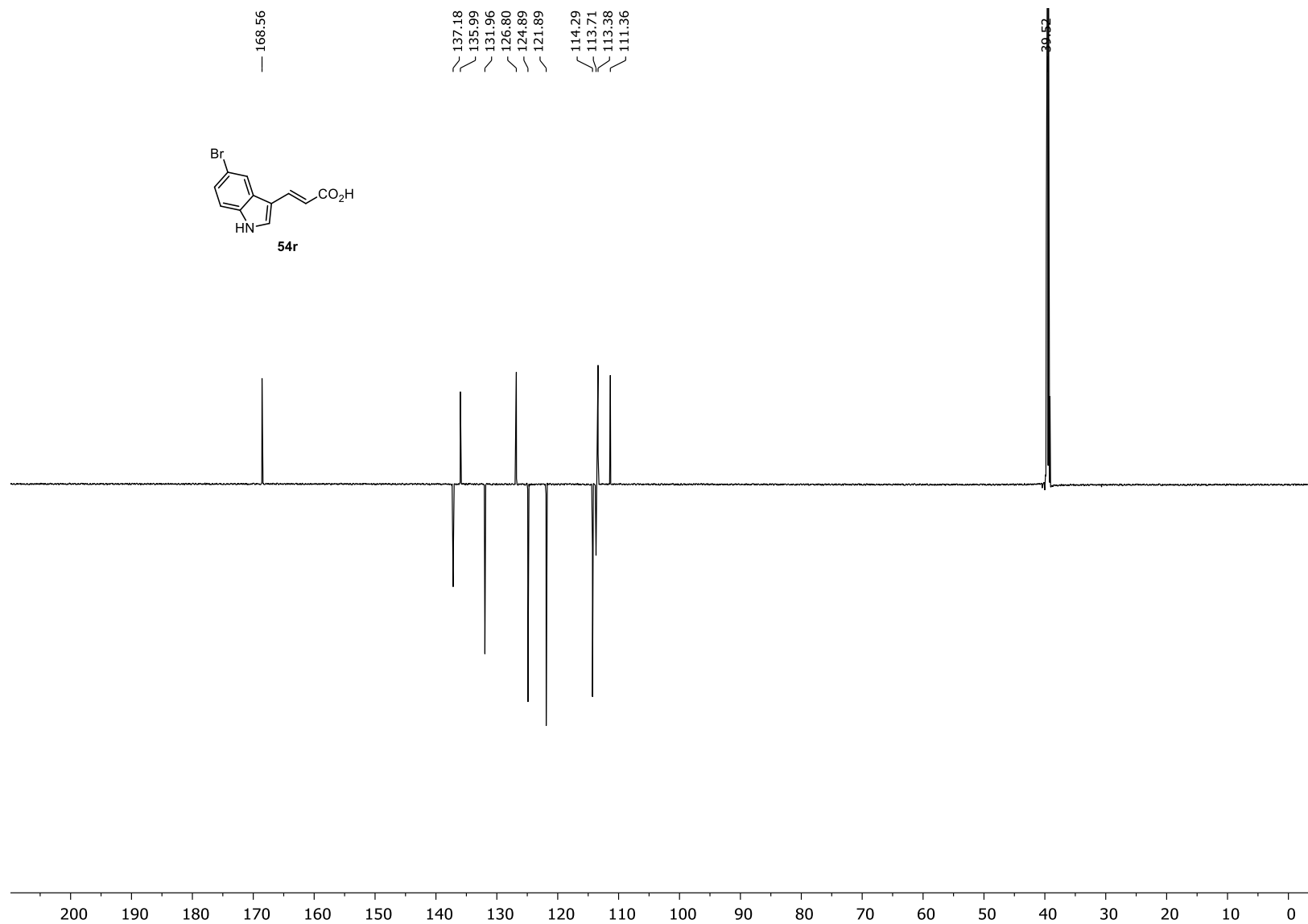
(*E*)-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acrylic acid (**54q**) (^{13}C NMR; 175 MHz; $\text{DMSO-}d_6$)



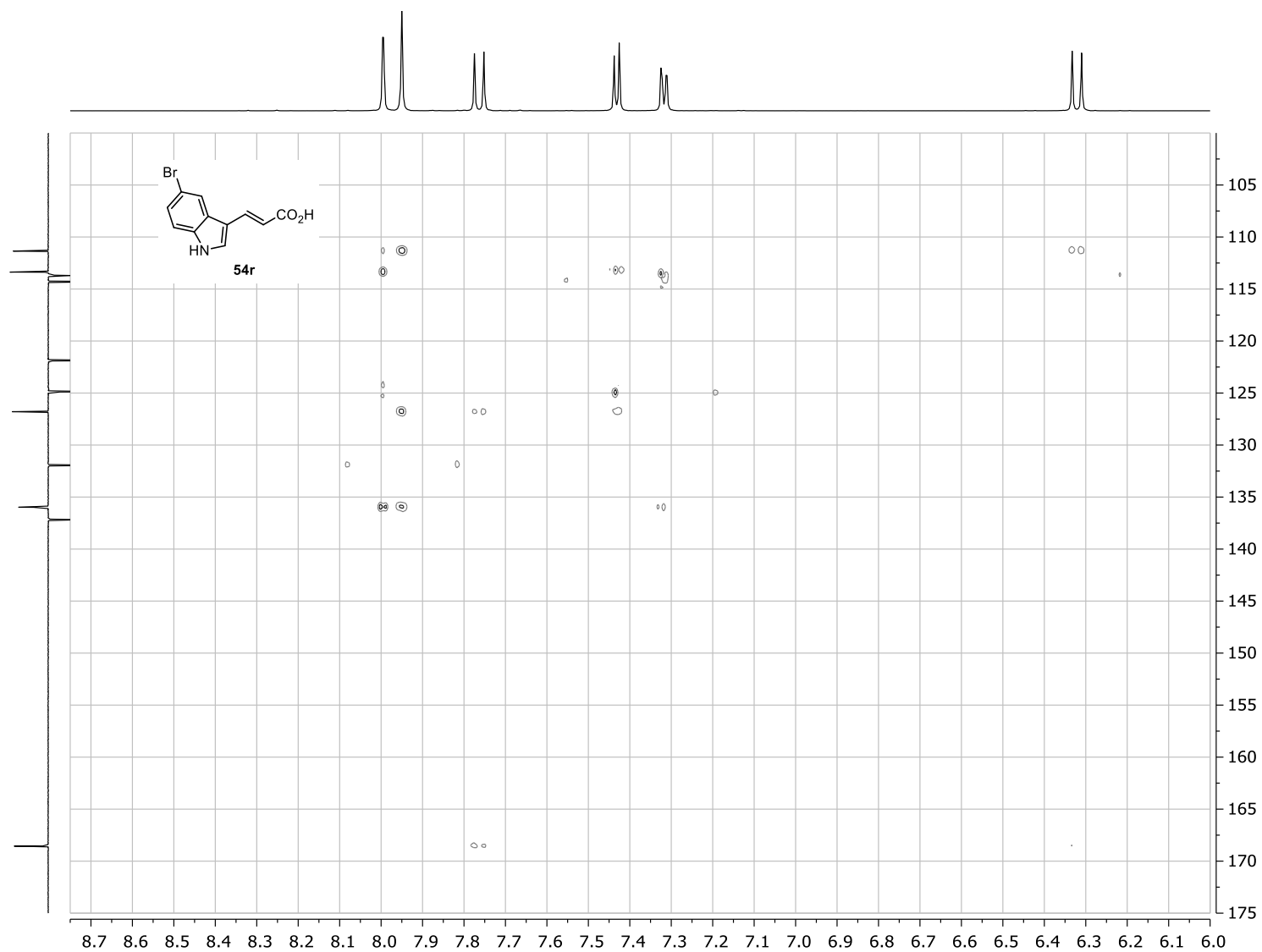
(*E*)-3-(5-Bromoindolyl)acrylic acid (**54r**) (^1H NMR; 700 MHz; $\text{DMSO}-d_6$)



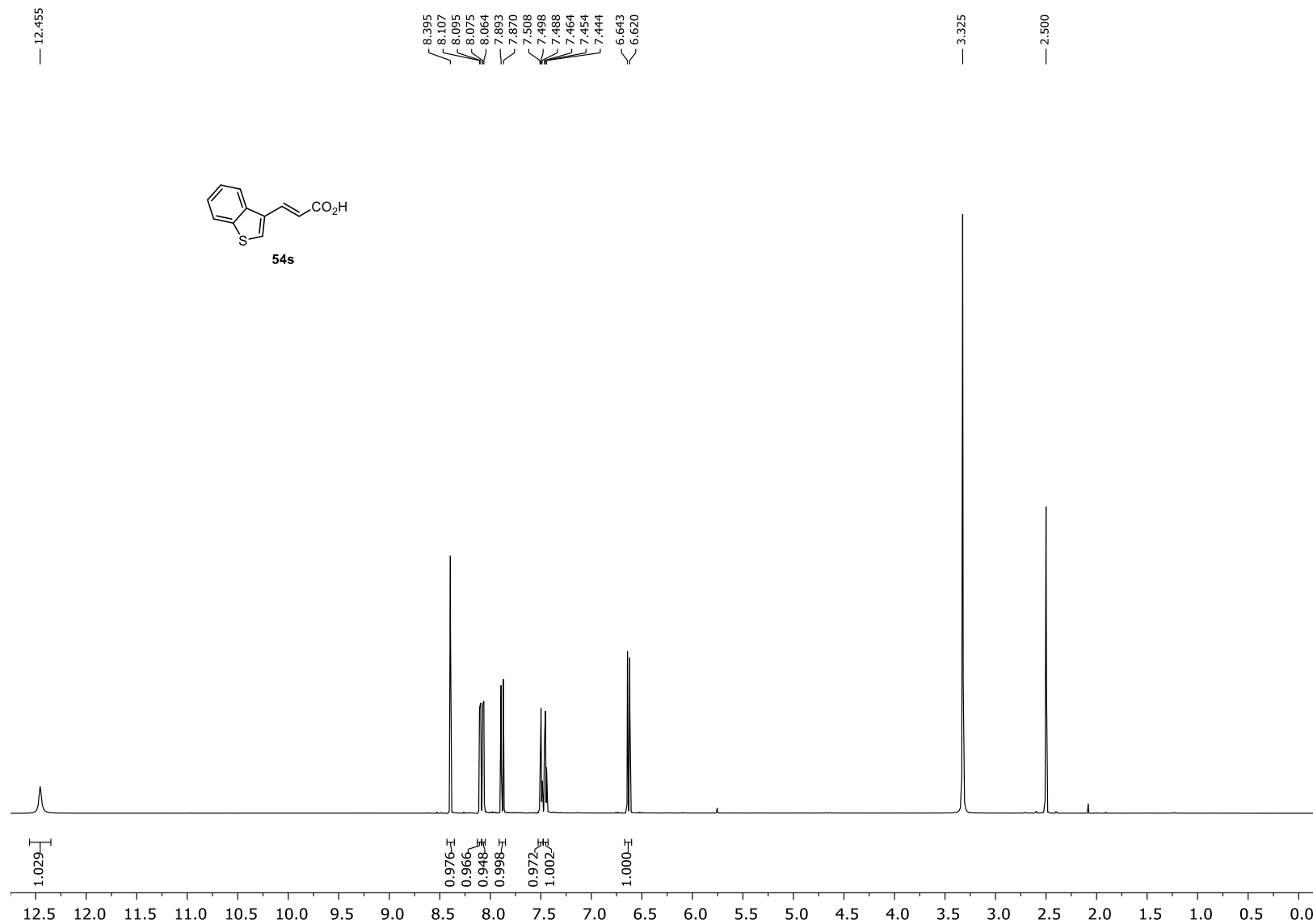
(*E*)-3-(5-Bromoindolyl)acrylic acid (**54r**) (^{13}C NMR; 175 MHz; $\text{DMSO-}d_6$)



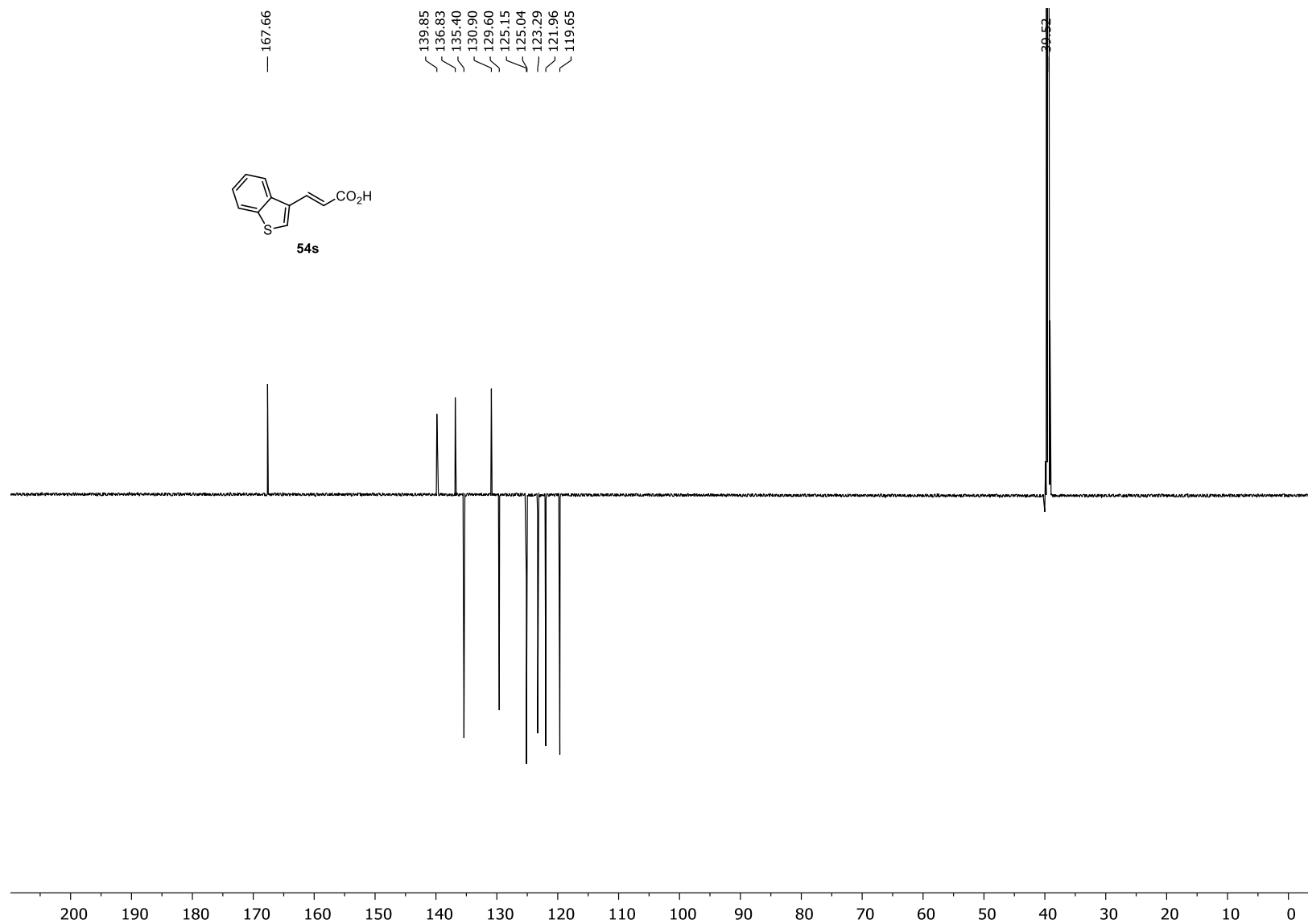
(*E*)-3-(5-Bromoindolyl)acrylic acid (**54r**) (HMBC; DMSO-*d*₆)



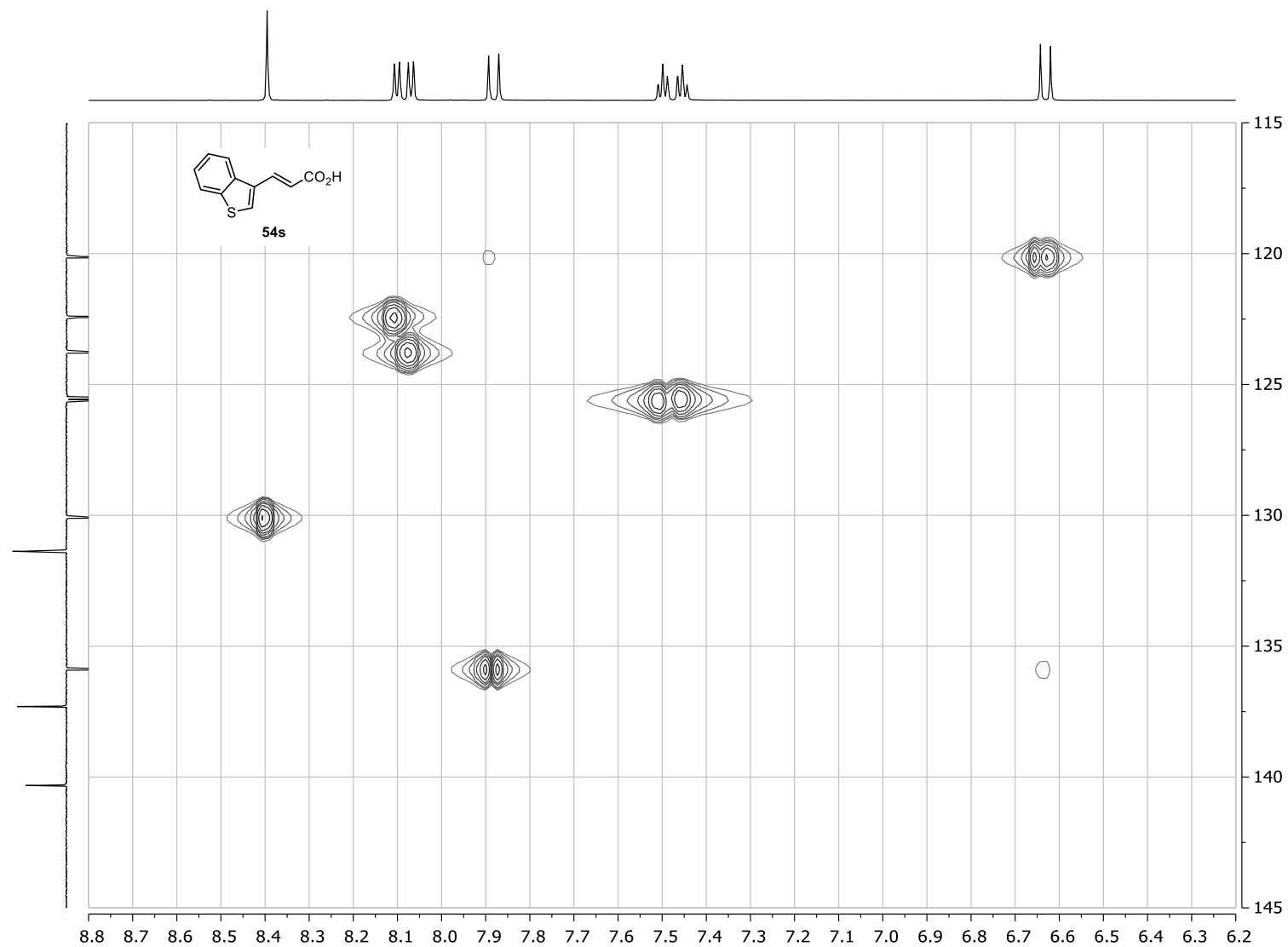
(*E*)-3-(3-Benzothiophenyl)acrylic acid (**54s**) (^1H NMR; 700 MHz; $\text{DMSO-}d_6$)



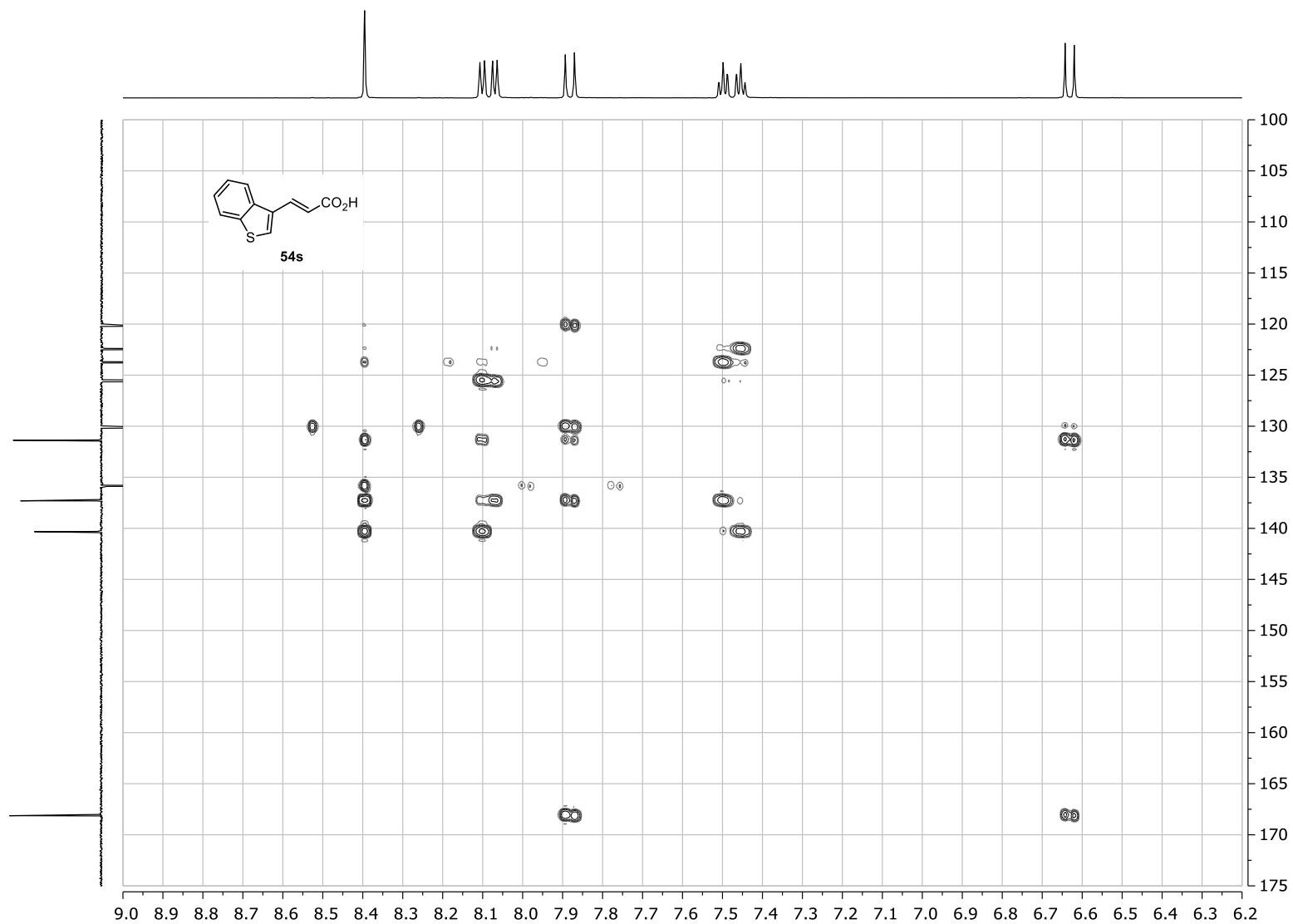
(*E*)-3-(3-Benzothiophenyl)acrylic acid (**54s**) (^{13}C NMR; 175 MHz; $\text{DMSO-}d_6$)



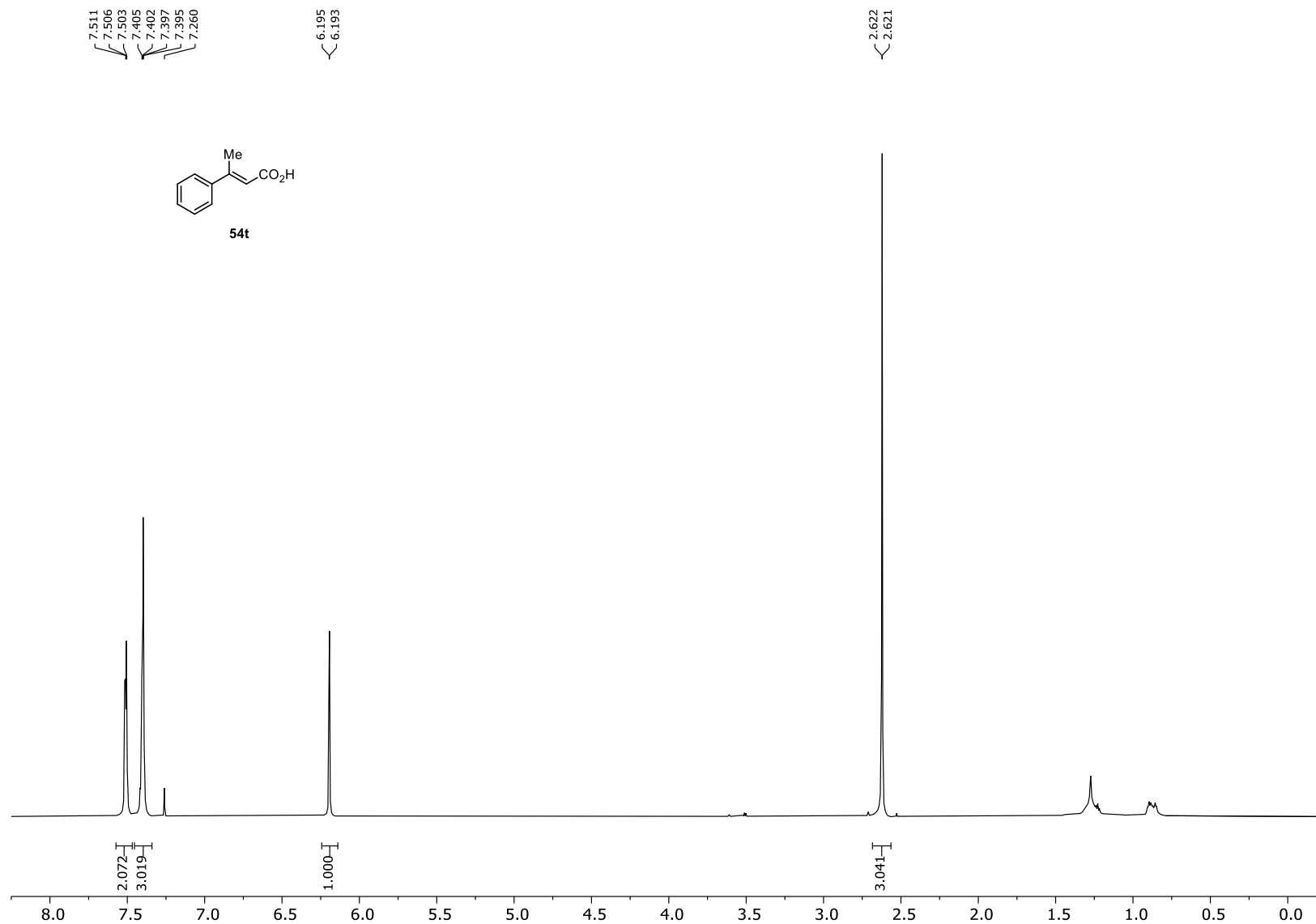
(*E*)-3-(3-Benzothiophenyl)acrylic acid (**54s**) (HSQC; DMSO-*d*₆)



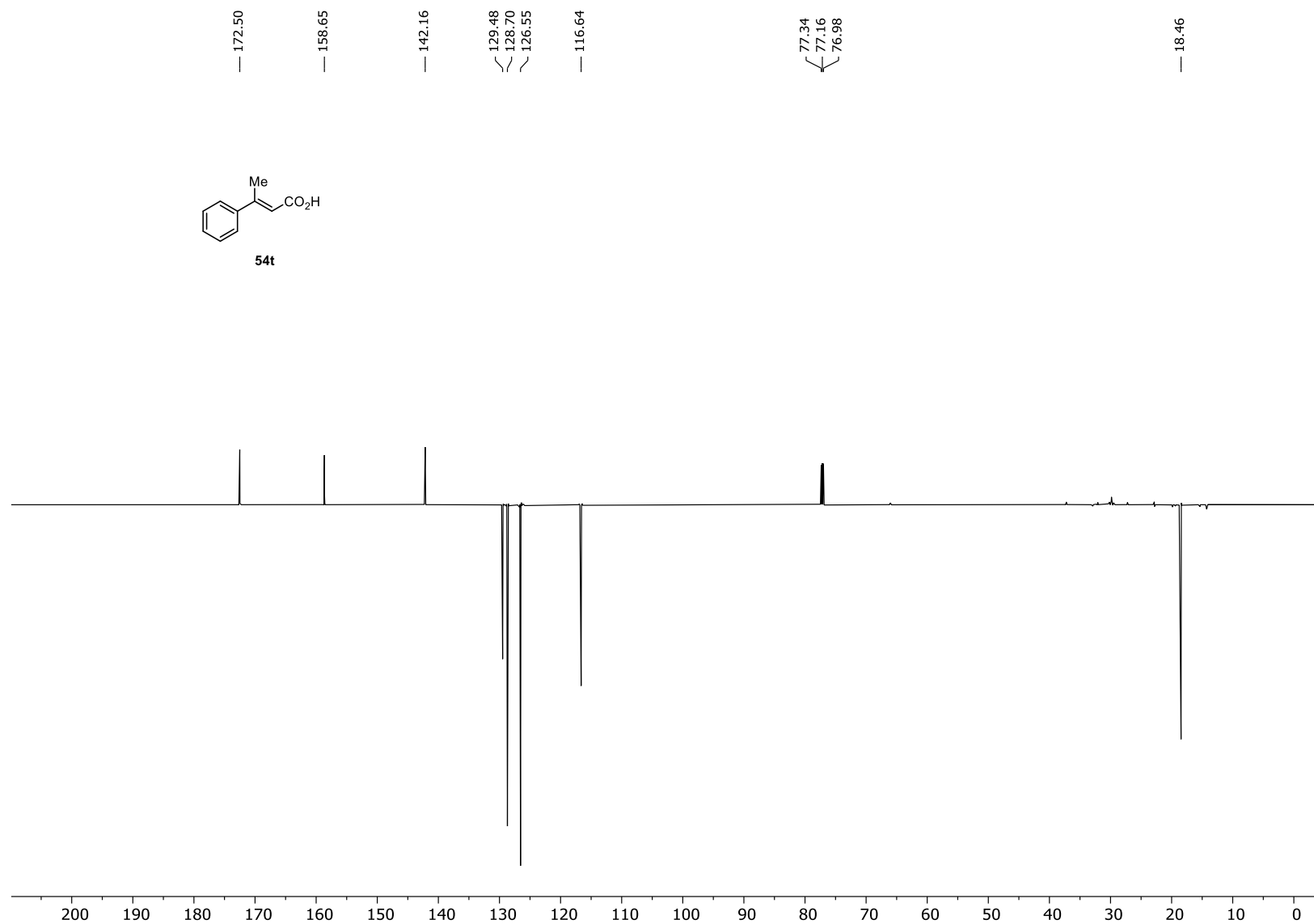
(*E*)-3-(3-Benzothiophenyl)acrylic acid (**54s**) (HMBC; DMSO-*d*₆)



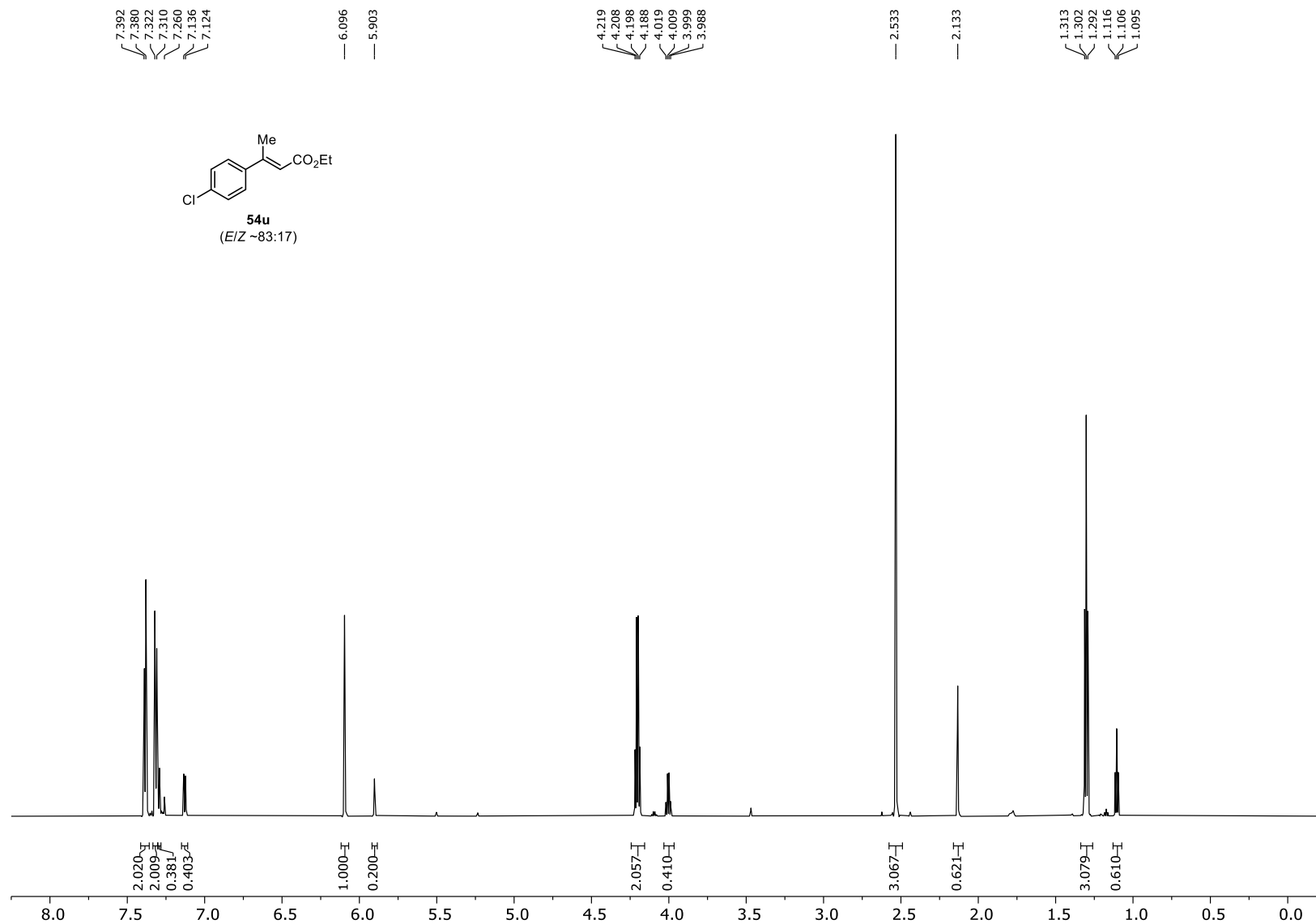
(*E*)-3-Phenylbut-2-enoic acid (**54t**) (^1H NMR; 700 MHz; CDCl_3)



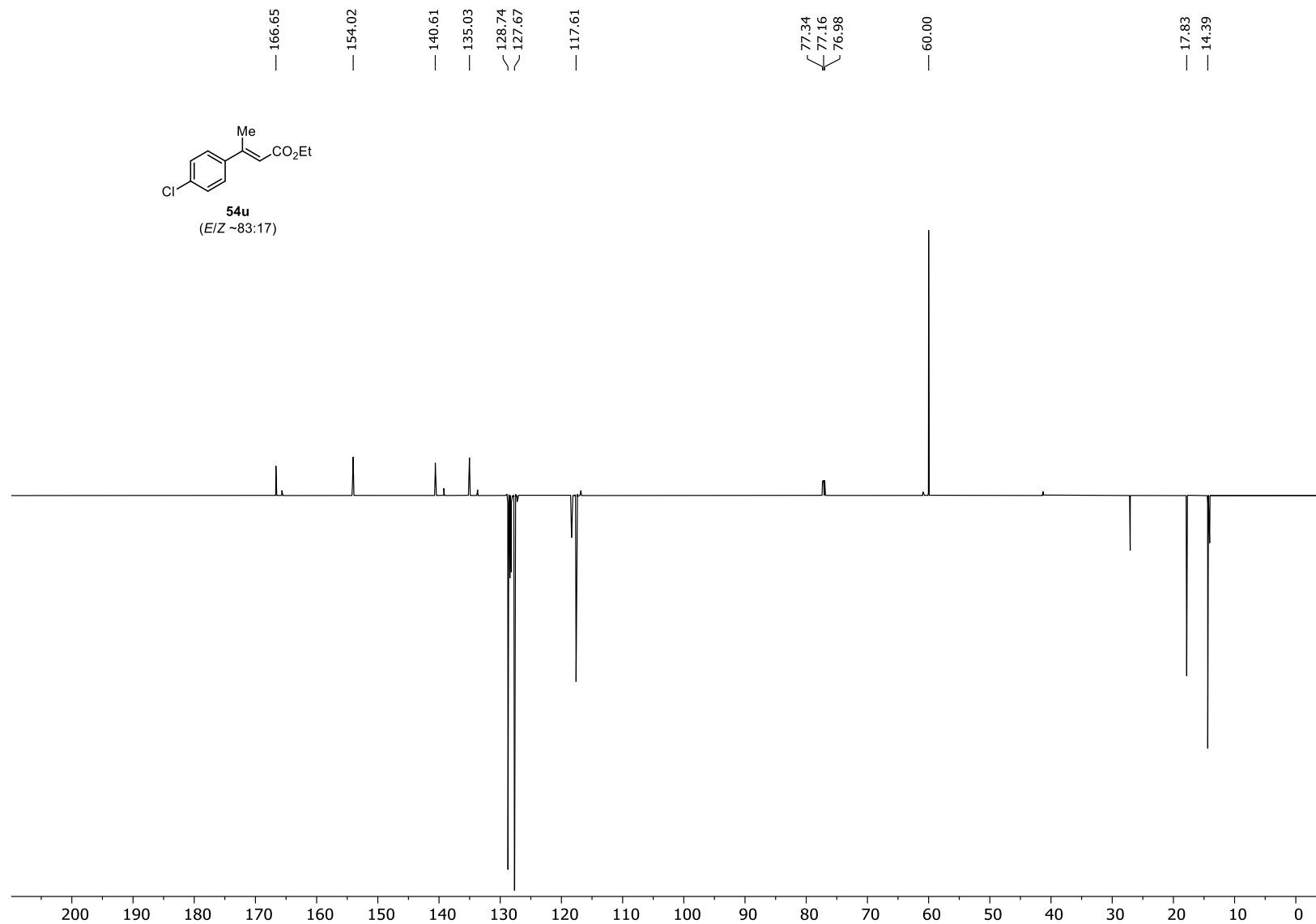
(*E*)-3-Phenylbut-2-enoic acid (**54t**) (^{13}C NMR; 175 MHz; CDCl_3)



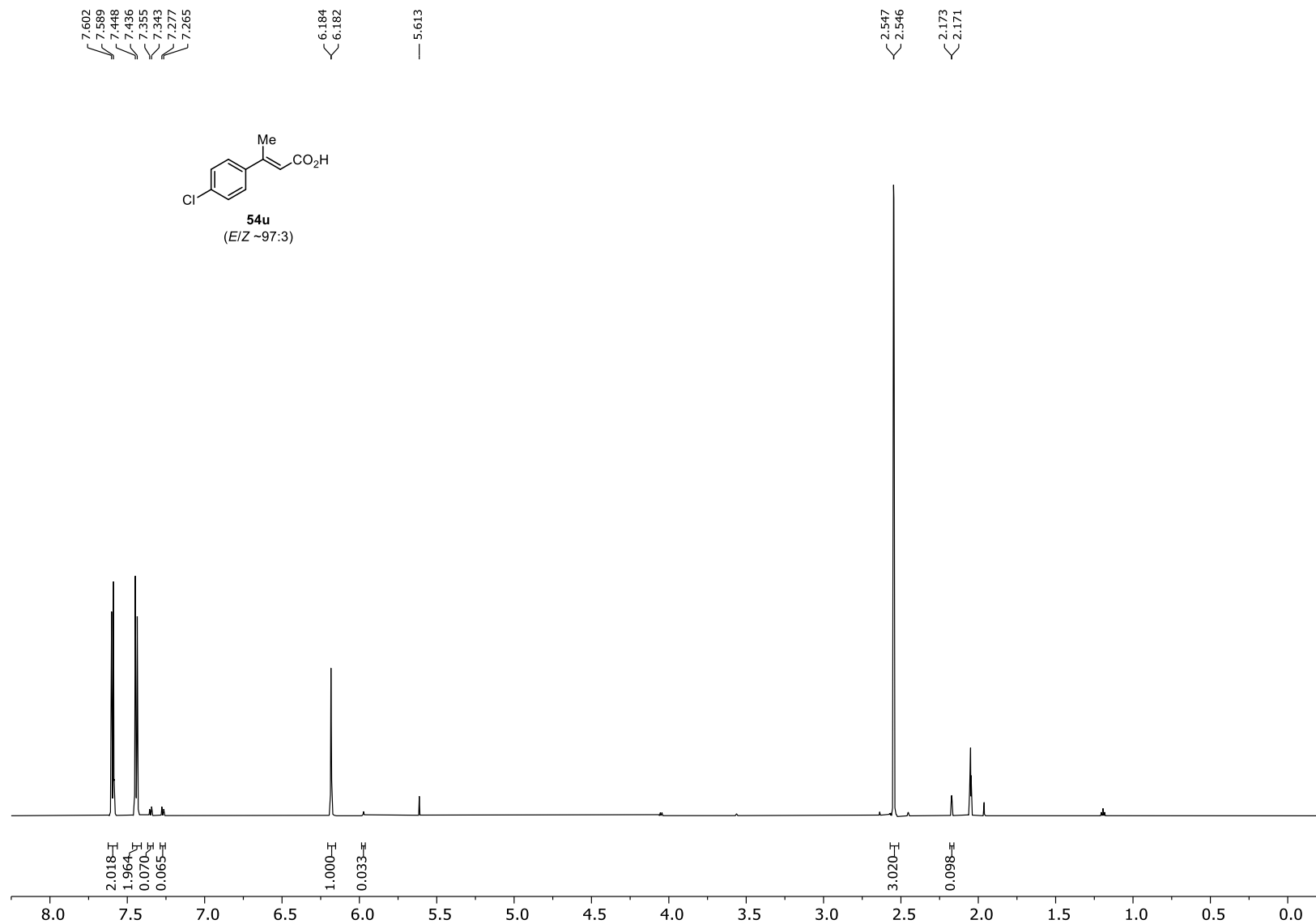
Ethyl (*E*)-3-(4-Chlorophenyl)but-2-enoate (**53u**) (^1H NMR; 700 MHz; CDCl_3)



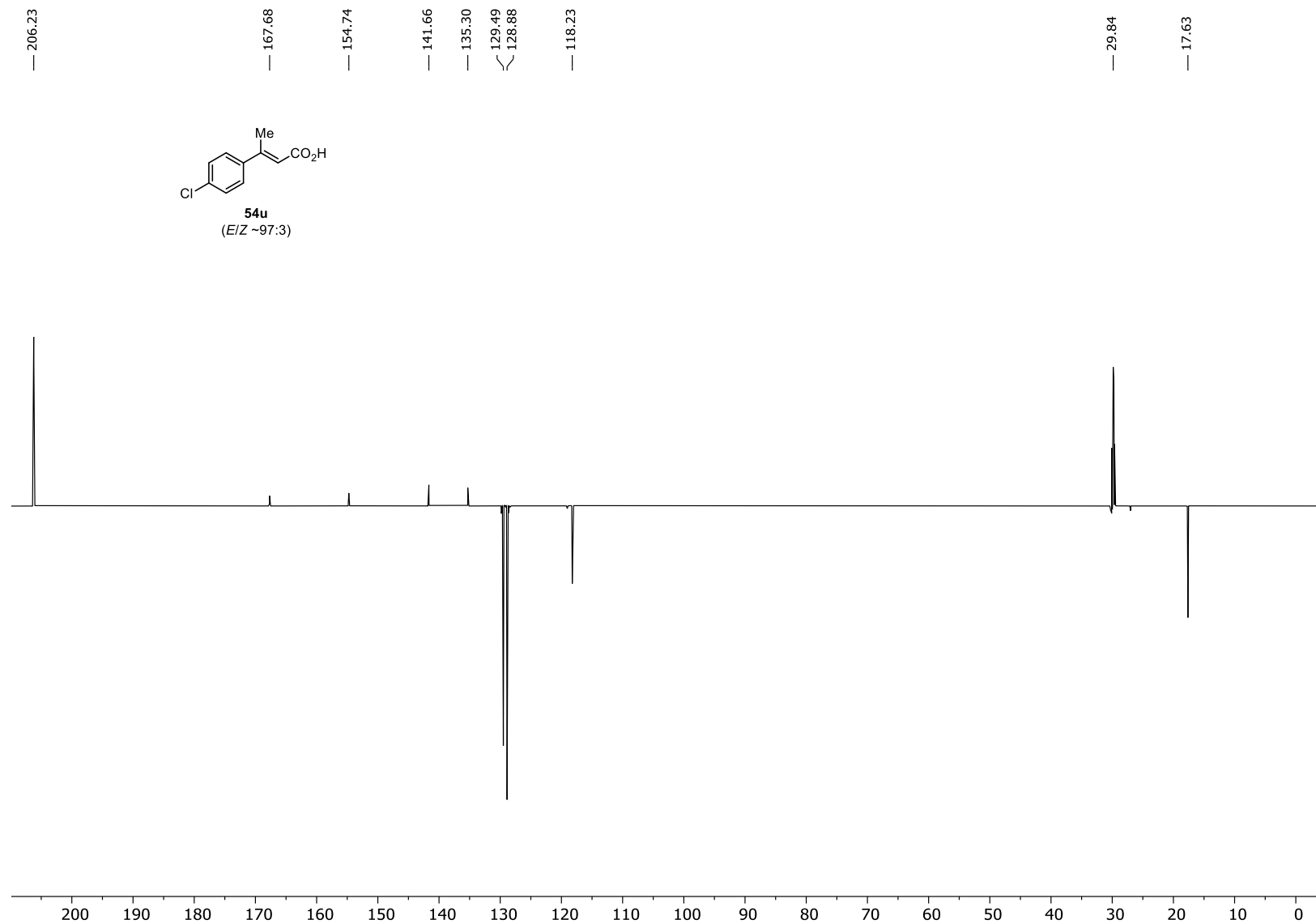
Ethyl (*E*)-3-(4-Chlorophenyl)but-2-enoate (**53u**) (^{13}C NMR; 175 MHz; CDCl_3)



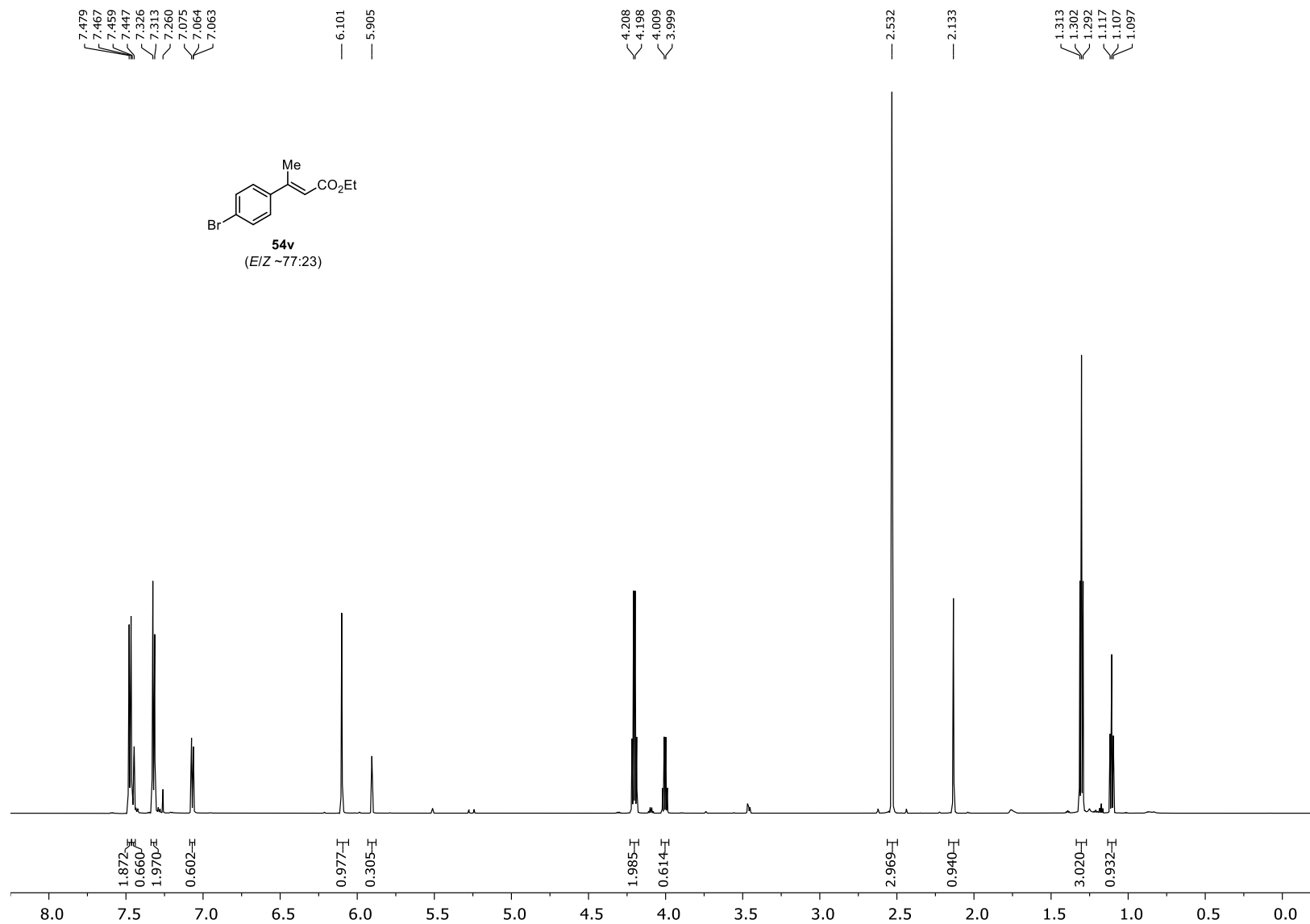
(*E*)-3-(4-Chlorophenyl)but-2-enoic acid (**54u**) (^1H NMR; 700 MHz; CDCl_3)



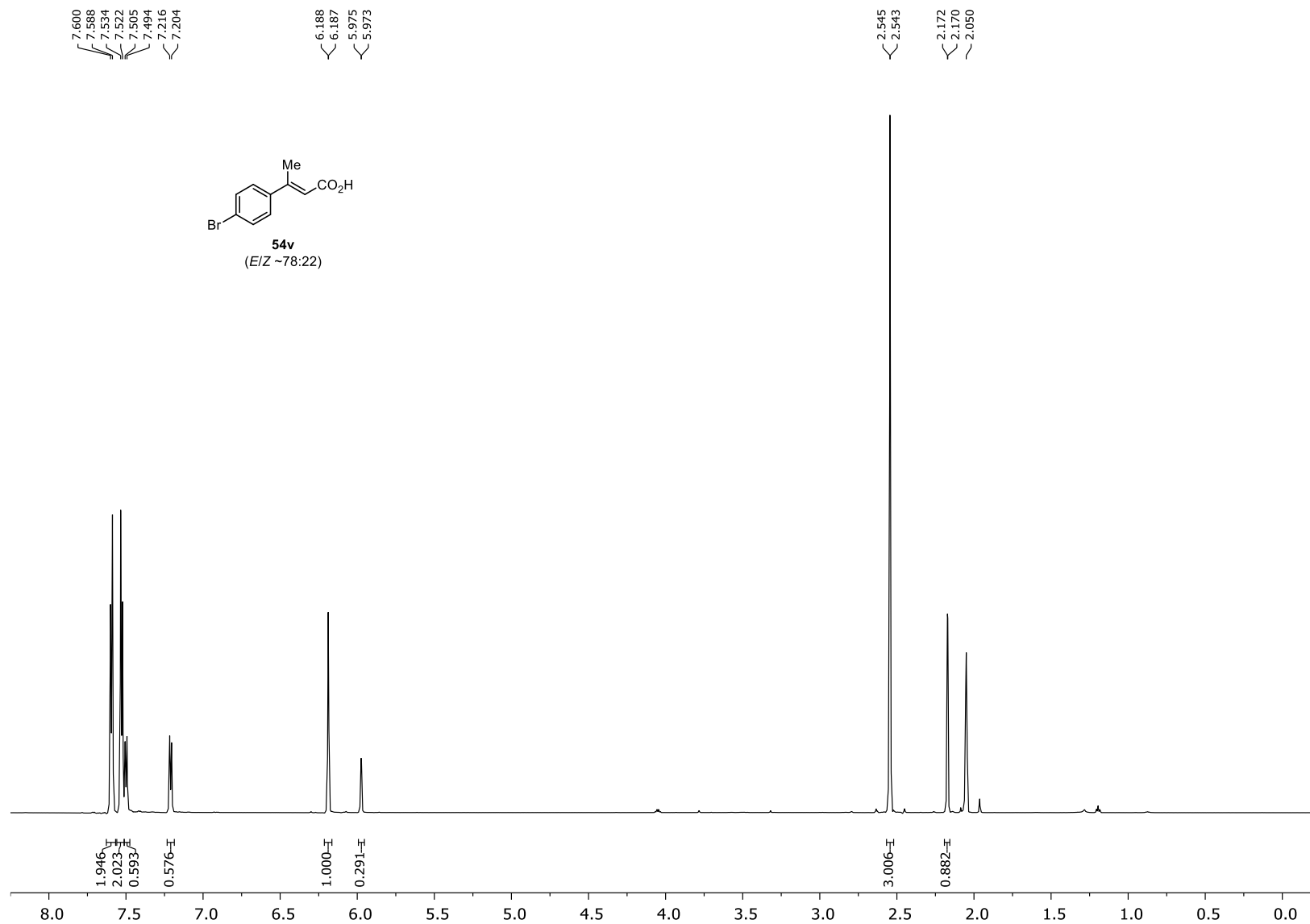
(*E*)-3-(4-Chlorophenyl)but-2-enoic acid (**54u**) (^{13}C NMR; 175 MHz; CDCl_3)



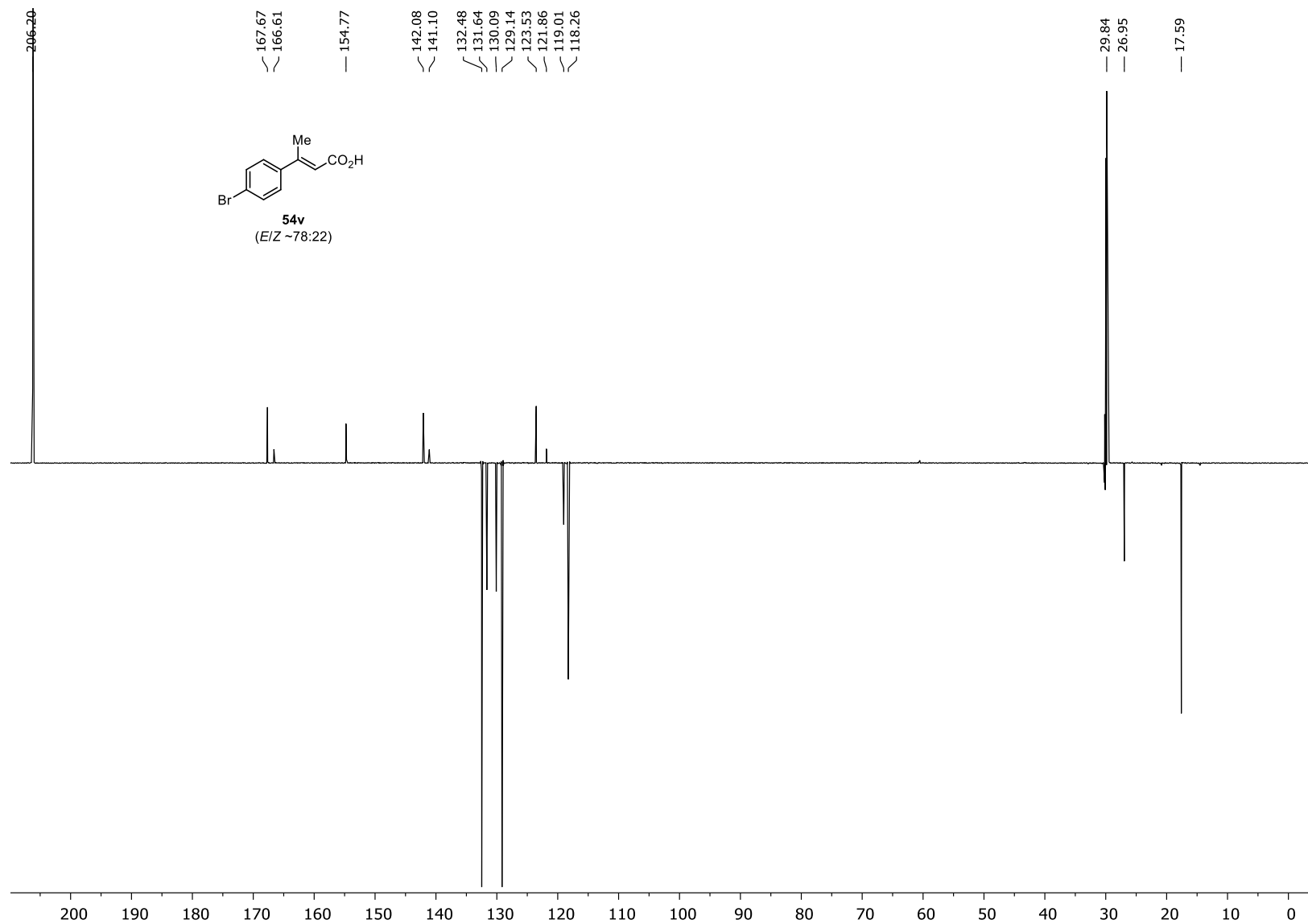
Ethyl (*E*)-3-(4-Bromophenyl)but-2-enoate (**53v**) (^1H NMR; 700 MHz; CDCl_3)



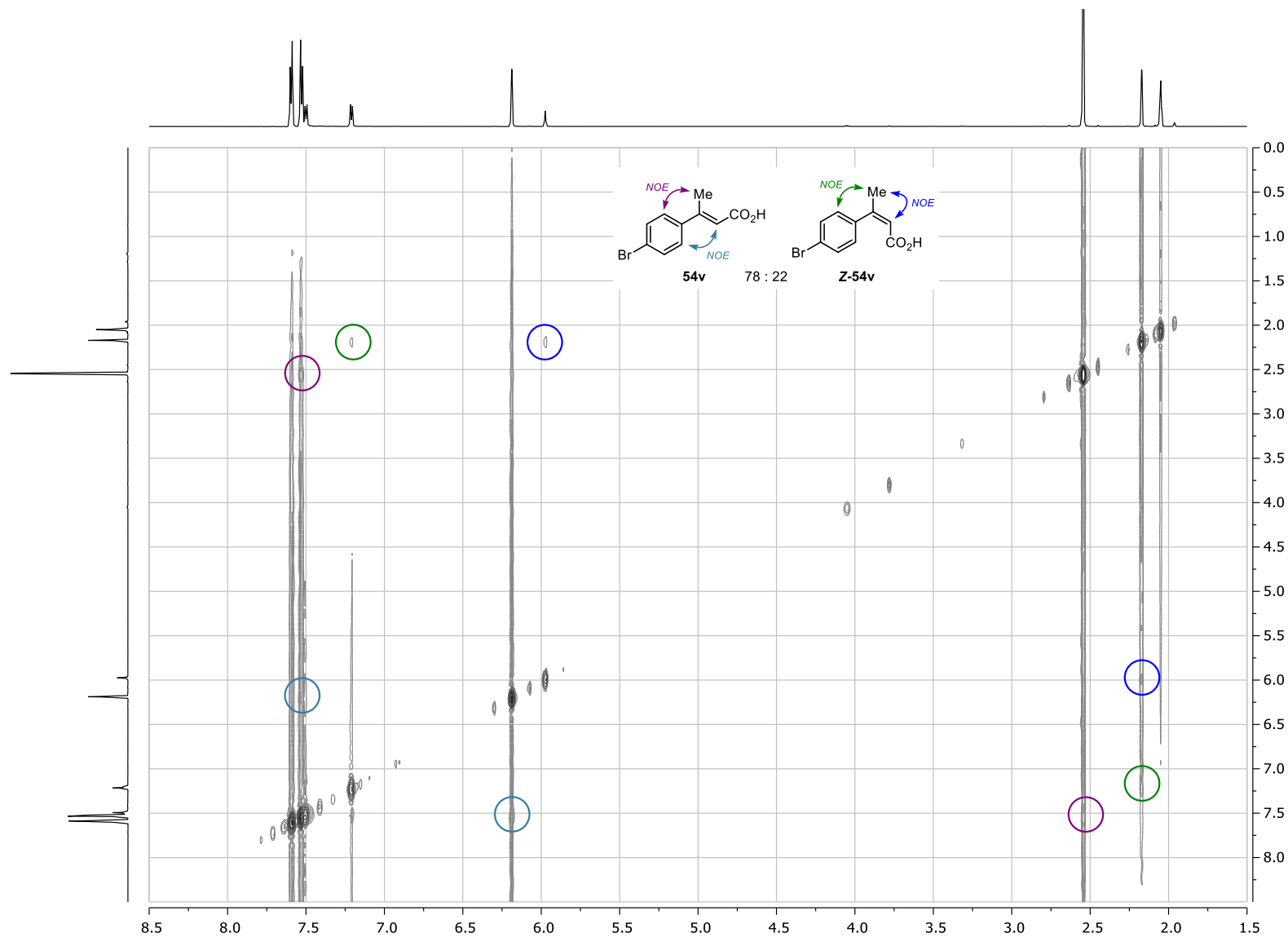
(*E*)-3-(4-Bromophenyl)but-2-enoic acid (**54v**) (^1H NMR; 700 MHz; acetone- d_6)



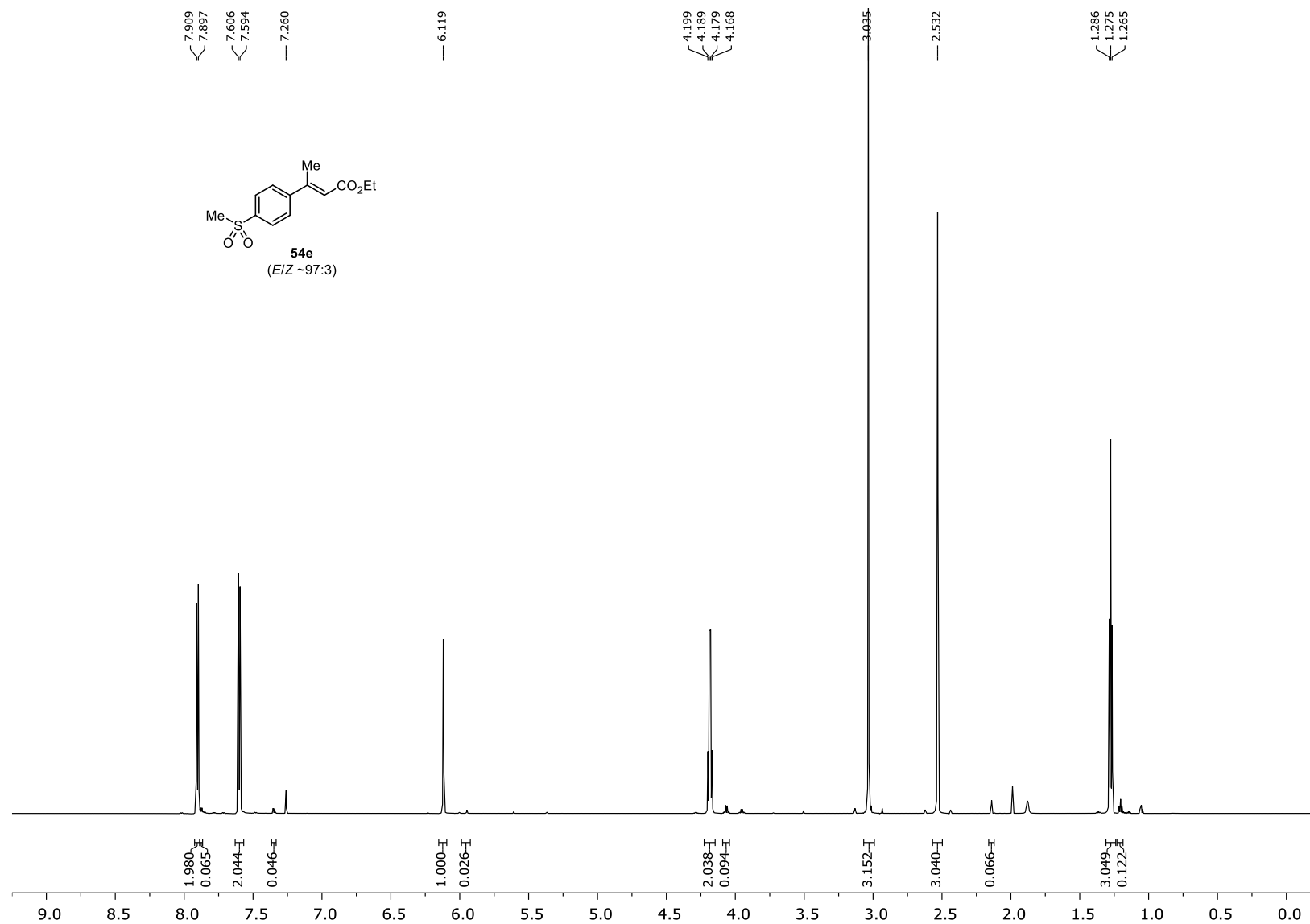
(*E*)-3-(4-Bromophenyl)but-2-enoic acid (**54v**) (^{13}C NMR; 175 MHz; acetone- d_6)



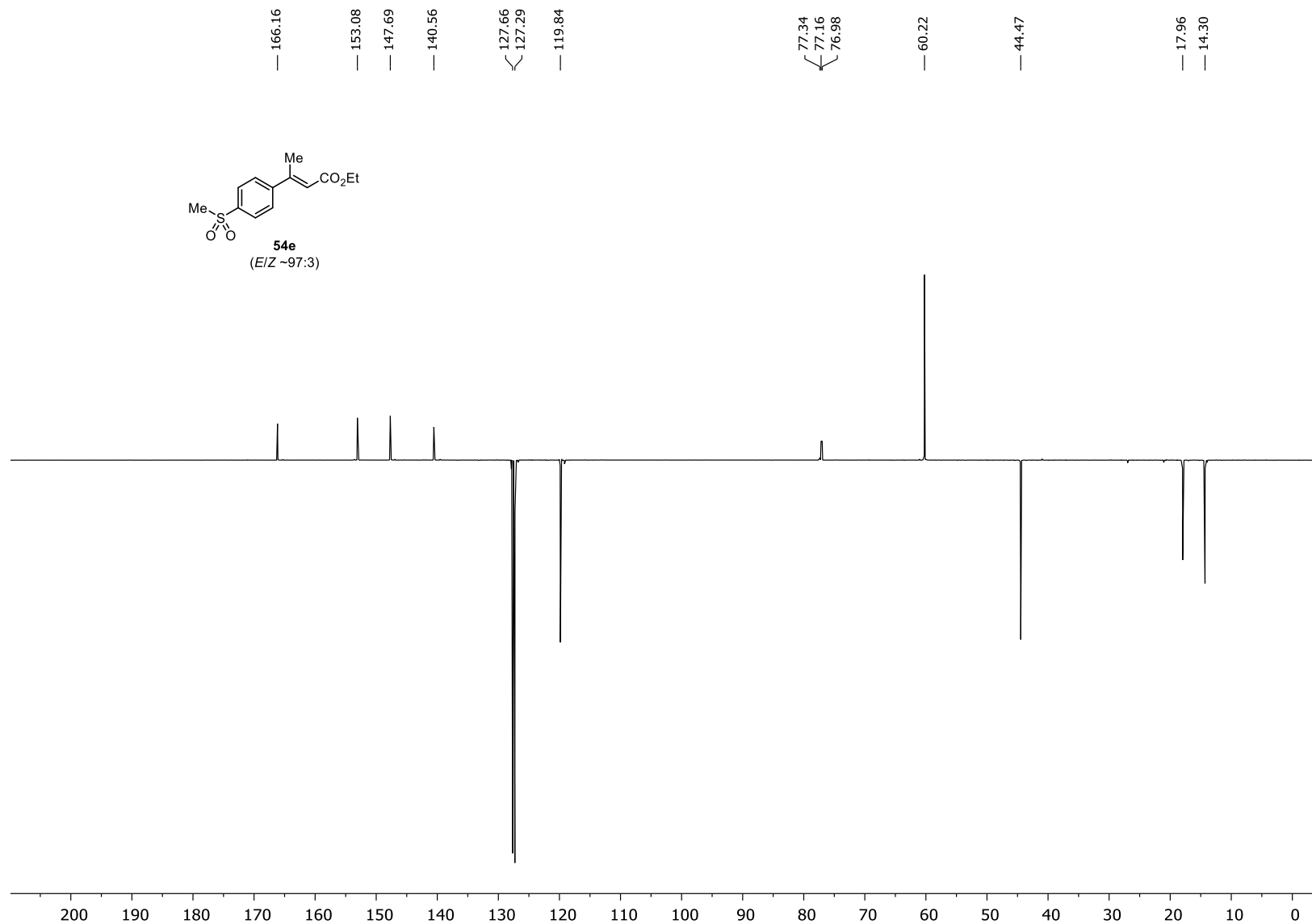
(*E*)-3-(4-Bromophenyl)but-2-enoic acid (**54v**) (NOESY; acetone-*d*₆)



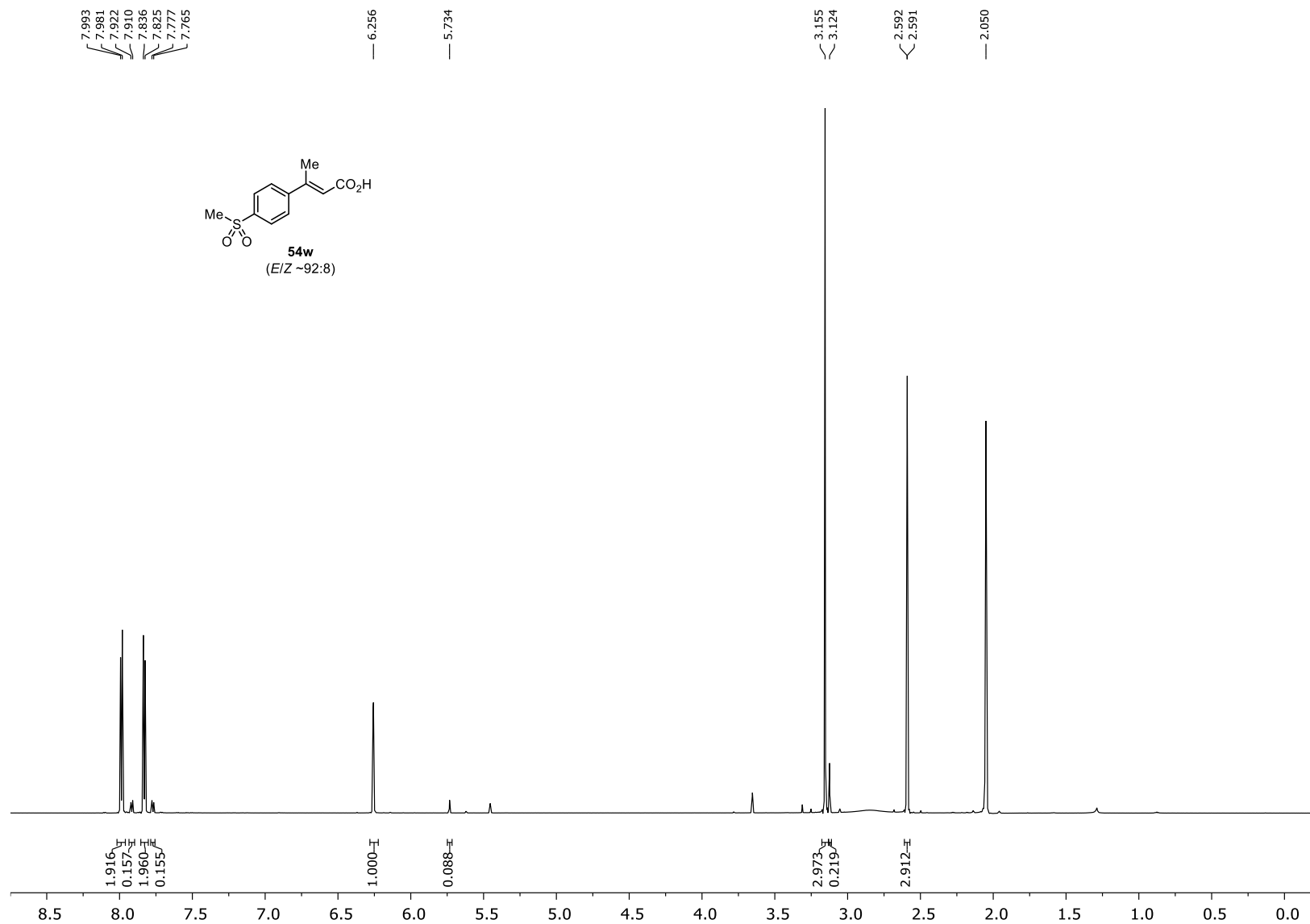
Ethyl (*E*)-3-(4-Methanesulfonylphenyl)but-2-enoate (**53w**) (^1H NMR; 700 MHz; CDCl_3)



Ethyl (*E*)-3-(4-Methanesulfonylphenyl)but-2-enoate (**53w**) (^{13}C NMR; 175 MHz; CDCl_3)



(*E*)-3-(4-Methanesulfonylphenyl)but-2-enoic acid (**54w**) (^1H NMR; 700 MHz; acetone- d_6)



(*E*)-3-(4-Methanesulfonylphenyl)but-2-enoic acid (**54w**) (^{13}C NMR; 175 MHz; acetone- d_6)

